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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

DELUCA, Vincent, M.
Rothwell, Figg, Ernst & Kurz
Suite 701 East
Columbia Square
555 13th Street N.W.
Washington, DC 20004
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 20 February 2002 (20.02.02)	
Applicant's or agent's file reference 2521-101.PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/US00/17810	**International filing date** (day/month/year) 29 June 2000 (29.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

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	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

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MEAGHER, John, F. 9293 Bayberry Avenue Manassas, VA 22210 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer François BAECHLER
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Copy for the Elected Office (EO/US)

PCT/US00/1781(

PATENT COOPERATION TREATY

10/009462

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

JOPPICH, Martin, Dr.
Hössle & Kudlek
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Date of mailing (day/month/year) 04 février 2002 (04.02.02)	
Applicant's or agent's file reference 2521-101.PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/US00/17810	**International filing date** (day/month/year) 29 juin 2000 (29.06.00)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

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3. Further observations, if necessary:

File reference has changed to 614 002 P-WO.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Carlos NARANJO Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

12

Applicant's or agent's file reference 2521-101.PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/17810	International filing date *(day/month/year)* 29 JUNE 2000	Priority date *(day/month/year)* 29 JUNE 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant INTERCET, LTD		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03 JANUARY 2001	15 OCTOBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ERIC STAMBER James R. Matthews Telephone No. (703) 305-8469

Form PCT/IPEA/409 (cover sheet) (July 1998)*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

national application No.
PCT/US00/17810

I. Basis of the report

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-35 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the claims:
pages 36-37 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the drawings:
pages 1-17 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the sequence listing part of the description: NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-5	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-5	NO
Industrial Applicability (IA)	Claims	1-5	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-5 lack an inventive step under PCT Article 33(3) as being obvious over Eisenberg et al.(5,594,637, hereinafter Eisenberg) in view of Keesee et al.(5,858,683 hereinafter Keesee) .

With respect to claims 1-5, Eisenberg teaches a database containing information relating to genetics and molecular biology(col. 2, lines 1-45); an operator interface for inputting into said system information and instructions corresponding to patient data(Fig 1); a plurality of program modules, each including at least one subroutine, for processing information and data inputted through said operator interface in conjunction with information obtained from said database, and outputting said information to said operator interface, wherein each of said program modules carries out descriptive and mathematical processes corresponding to different levels of human diseases biological processes, and information generated by modules performing lower level processes also is outputted to modules performing higher level processes, whereby predictive diseases as well as past origin of diseases are provided and an output device for communicating results of subroutine processing to a user(Figures 1-3). Eisenberg does not specifically teach that the disease being simulated is the occurrence of cancer in the human body. On the other hand, Keesee teaches a method and system for detecting and treating cancer in an individual(Abstract). It would have been obvious to a person of ordinary skill in the art at the time of Applicant's invention to have included simulating the occurrence of cancer in the human body because such a modification would allow for treatment of cancer in an individual and for monitoring the efficacy of such treatment in the individual(in Keese, col. 2, lines 60-62).

NEW CITATIONS

NONE

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): A61B 5/00; C12Q 1/68; G06F 17/30, 15/18, 159/00; 17/60; G01N 33/53 and US Cl.: 435/7.1, 6; 705/2, 3; 706/45; 16; 707/1, 3;

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/17810

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :435/7.1, 6; 705/2, 3; 706/45; 16; 707/1, 3;
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/7.1, 6; 705/2, 3; 706/45; 16; 707/1, 3;

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,594,637 A (EISENBERG et al) 14 January 1997, entire document.	1-5
Y	US 5,858,683 A (KEESEE et al) 12 January 1999. entire document.	1-5
A	US 5,794,208 A (GOLTRA) 11 August 1998, entire document.	1-5
A	US 5,800,350 A (COPPLERSON et al) 01 September 1998, entire document.	1-5
A	US 5,756,294 A (WHITE et al) 26 May 1998, entire document.	1-5
A	US 5,724,580 A (LEVIN et al) 03 March 1998, entire document.	1-5

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
13 AUGUST 2000	03 OCT 2000

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	TODD VOELTZ
Facsimile No. (703) 305-3230	Telephone No. (703) 308-9724

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/17810

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,867,821 A (BALLANTYNE et al) 02 February 1999, entire document.	1-5
A	US 5,790,761 A (HESELTINE et al) 04 August 1998, entire document.	1-5
A	US 5,517,405 A (MCANDREW et al) 14 May 1996, entire document.	1-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/17810

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

A61B 5/00; C12Q 1/68; G06F 17/30, 15/18, 159/00; 17/60; G01N 33/53

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

EAST.STN
educating,estimating,describing,predicting,cancer,metastases,peocess,stages,develops,presence,algorithm,mathematical,programs,software

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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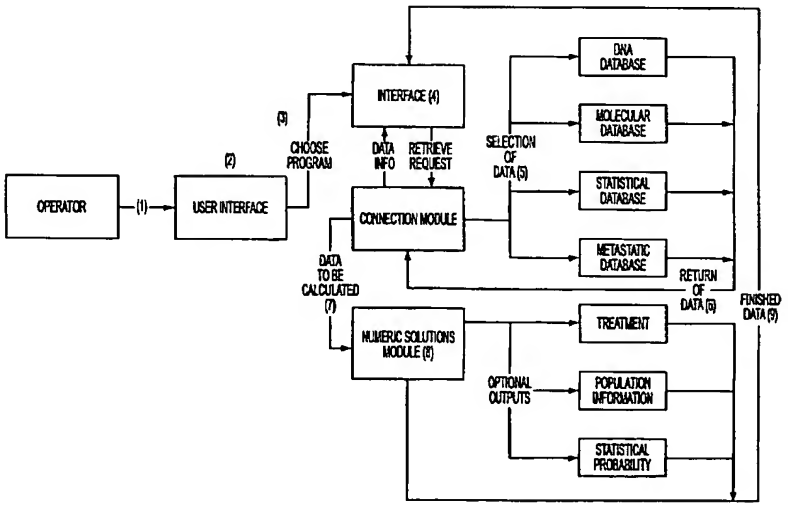
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian

[Continued on next page]

(54) Title: HUMAN CANCER VIRTUAL SIMULATION SYSTEM



(57) Abstract: A series of mathematical algorithms and descriptive process applies information from molecular biology and medical science to simulate the occurrence and metastases of cancer in the human body. The human cancer virtual simulation or HCVS, engine is a series of software program modules (5), run on a computer, containing the necessary medical information needed for a simulation of the occurence and metastases of cancer in the human body. These programs allow the user to enter individual patient information (2) into them producing data results in the form of statistical and predictive reports along applicable time lines into the future or of the past. This configuration allows selection of modules, subroutines parameters and patient input (2) to be entered into the engine selectively. Depending on the selection the user (3) can move forward or backward in time to generate simulated human cancer results (biological information, etc.).

WO 01/000083 A1

patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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— *with international search report*

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6 September 2002

(15) Information about Corrections:
see PCT Gazette No. 36/2002 of 6 September 2002, Section II
Previous Correction:
see PCT Gazette No. 04/2002 of 24 January 2002, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

HUMAN CANCER VIRTUAL SIMULATION SYSTEM

BACKGROUND OF THE INVENTION

Field of the Invention

This invention generally relates to computer-implemented simulation systems using mathematical and descriptive algorithms and data, and more specifically relates to a computer-implemented system that simulates events of cancer in the human body. The invention uses computer-generated simulations of biochemical and morphological human cellular transformation from normal cells to metastatic tumors and provides where, when and how the distant metastases of cancer can take place. The invention uses information from molecular biology and medical science to model and predict cell to cancerous tumor to metastatic occurrence using parameters related to living organisms.

Background and Prior Art

The simulation of human biological and medical processes, and in particular human cancer processes from cell to tumor to distant metastatic sites would provide many advantages to students, researchers, physicians and patients. Currently, no mathematical and descriptive approach exists that can provide practical results to students, researchers, physicians and their patients about the origin and future behavior of cancer in the human body. At present, cancer is diagnosed and treated in real-time and in the real world based on the best clinical information available to health care providing teams. The present invention improves this situation by utilizing a mathematical and descriptive process to develop vital information for a human cancer virtual simulation, thus providing a computer based and interactive environment in which to examine origins, current characteristics and future outcomes of the human cancer process.

One or two models currently are under development to simulate normal cellular processes and describe biologic properties of normal cells, not human cancer cells as proposed in this invention. Some models are under construction based on scanned images or construction of tumors in a 3- dimensional computer simulation. These are representational models and differ from the present invention in that they do not contain predictive, interactive or retroactive analytical subroutines capable of modification of the program output in real time. No descriptive or mathematical engines have been developed to depict a cell undergoing transformation from a normal cell and distant cancer sites within the human body using specific molecular biological cellular changes for human cancer. The simulation engine that is provided by the present invention has the specific ability to simulate human cancer behavior and in an interactive environment that has practical diagnostic, research and treatment approaches regarding the origin of human cancer and possible future behavior of cancer in the human body.

SUMMARY OF THE INVENTION

The present invention provides a model that simulates human cancer cell behavior for medical and physiological functions has unique educational value. It provides medical students the ability to repeat a lesson. The invention reduces the use of animals and the concomitant uncertainty with animal information extrapolated to human beings. The invention can improve medical education by offering a dynamic flexible learning environment never before possible due to the small number and availability of real live patients with cancer cases

at all stages of disease. It allows students to make some therapeutic choices and examine the efficacy and results in a virtual environment. It links probability to the medical learning process in a hands on way. No model can replace the live patient experience; however the invention augments it and ethically provides a realistic, yet forgiving environment for learning. It provides students opportunities to make choices and to learn from them.

For researchers, the interactive human cancer model according to the present invention provides descriptive simulations useful for the study of new and current pharmaceutical applications in cancer treatment, and can reduce costs and improve therapeutic interventions. A computer based mathematical and descriptive engine of the molecular to metastases process can provide simulated outcomes in a non-clinical environment to help make decisions when experimental clinical applications are being considered. Some of the interfaces envisioned in the invention will allow drug response to be modeled at the molecular, cellular, tissue, and metastatic levels, with simulated results. The results will be generated around biochemical parameters of importance for a drug's effectiveness or to help identify the patient's individual characteristics that could benefit from a drug's treatment. The invention has the ability examine timing cycles for drug delivery to improve the effectiveness of anti-cancer action, enable the modeling of a drug's effects on a tumor at multiple times using the invention under a variety of conditions enhancing the statistical and probable confidence of outcome.

The human cancer virtual simulation engine is capable of continual refinement and improvement in predictive accuracy through medical research by comparing and contrasting results from the engine with results from the actual clinical settings. This allows testing, modification and improvement of the engine's mathematical algorithms as new medical and scientific discoveries are uncovered. The invention, because it is a computer based mathematical and descriptive engine model of the human cancer process, provides a researcher with a powerful tool because it can be experimented with and modified using information from past research and clinical studies. This allows a researcher to test new and current hypotheses and algorithmic expressions of the human cancer process. The invention thus provides a means to test ideas and improve scientific knowledge in a clinical or non-clinical environment using retrospective information before clinical trials on real patients begin. If new and improved assumptions add new algorithms, based on molecular biology and medical science, the invention can be modified and improved in its ability to provide useful information to students, researchers and physicians in understanding and predicting the path of human cancer in the human body.

For treatment of the patient by a physician, the simulation system according to the invention will allow input of clinical findings specific to an individual cancer patient to be entered into the engine. The function of allowing input will allow the physician flexibility to make a range of judgments of medical importance to be entered into the engine and then the engine will develop a probable and statistical prediction of several possible clinical outcomes. The possible clinical outcomes will include where or when high concentrations of cancerous emboli will cause metastases to appear in the human body. Once a tumor and its location is discovered, the engine will allow a simulation backwards in time to determine the possible range of times for cancer or tumor origin, cellular biochemical changes that possibly gave rise to carcinogenesis, vascular formation within the tumor and micro metastatic behavior.

The engine's results and reports will be of importance in understanding the etiology of cancer in an

individual patient and examining treatment options and evaluating prognosis. The reports from the invention will potentially allow diagnostic testing to be performed in localized areas, looking for smaller cancer presence, increasing the likelihood that earlier, less expensive, less invasive treatment can be performed, thus improving the quality of treatment outcomes. The invention will provide useful information to assist the physician with short term and long term patient follow-up and to compare and contrast the patient's response to treatment in a real clinical setting with simulations developed by the human cancer virtual simulation engine. The engine will allow interface and insertion of new information at any time along a time line permitting the module's in the engine to be modified to conform to new assumptions on a daily, weekly, monthly or yearly basis. The engine would become another tool in the arsenal of the oncologist for examining possible outcomes of treatment as they develop treatment regimes.

The simulation system is progressive and is capable of being modified and improved in conjunction with new advances in molecular biology and medical science. The continual updating of databases to improve the calculation abilities of the engine and its subroutines, described later in this application, is one way to accomplish this. Another dynamic aspect of the invention is that the descriptions generated from some parts, specifically the molecular driven portions of the metastatic, tissue, and tumor modules will provide estimations of tumor size, and location in the human body and other cancer tumor morphology characteristics that can be coupled with visualization, display and imaging technology. As described hereinafter, the invention describes processes involved in cellular transformation from a normal cell then to a cancerous tumor and describe probable metastases elsewhere in the human body. The invention also has the capability to provide projections about the origin and future of human cancer manifestations.

The invention synthesizes fundamental molecular biology and medical knowledge into a simulation system. The system allows questions to be asked and provides answers of practical value to the human cancer process. It provides a virtual description beyond the present tense, such as possible future metastatic sites and past origin of the human cancer process. As new discoveries are made certain algorithms can and will be modified and improved, but the fundamental workings of the engine will remain the same.

The principal object of the present invention is to provide a descriptive and mathematical engine for a human cancer virtual simulation system that applies information from molecular biology and medical science to simulate the occurrence and metastases of cancer in the human body. The invention uses a computer as an information-input apparatus and a visual monitor for output. A series of software program modules employing a system of specially written programs and databases are employed which allow the user to enter into the programs individual patient information thereby producing information, results and reports about simulated human cancer.

The invention has two major configurations, medical and educational applications. The medical application configuration generates human cancer simulation information, reports and statistical and predictive results along applicable time lines of the future or the past. This configuration allows selection of modules, subroutines, parameters, and patient input to be entered into the engine selectively. Depending on the selection, the user can move forward or backward in time to generate simulated human cancer results and reports. The system provides the capability to predict future courses of human cancer to describe the possible origin of human cancer in a patient. The results from the engine is virtual in that it produces simulated descriptions of human

cancer in the body in the present, the past and the future.

The educational configuration will use pre-programmed information, but allows limited interaction for medical student educational purposes. The medical applications configuration will allow diagnostic, treatment and research human cancer simulations to be performed.

Brief Description of The Drawings

Fig. 1 is a block diagram illustrating the operator's relationship to the engine including data flow;

Fig. 2 is a block diagram illustrating the operator's relationship as described above with the engine configurations;

Fig. 3 is a block diagram of the overall engine module structure according to one preferred embodiment of the invention;

Figs. 4-10 are flow diagrams illustrating the various subroutines for each of the modules of the simulation engine according to the present invention;

Fig. 11 is a block diagram illustrating data flow interactions of manual user input with the various modules of Fig. 3 and a patient information database;

Fig. 12 is a block diagram illustrating data flow interactions between the various modules of Fig. 3;

Fig. 13 is a block diagram of a system for receiving data from external data sources, and analyzing and distributing the received data into various data types for incorporation into model algorithms according to one preferred embodiment of the invention;

Fig. 14 is a flow diagram detail of the cell cycle routine shown in Fig. 3 according to one preferred embodiment of the invention; and

Fig. 15 is a flow diagram of an algorithm for simulating cell protein production within a cell life cycle, according to one preferred embodiment of the invention.

Detailed Description of the Preferred Embodiments

Description of Databases

The Human Cancer Virtual Simulation (HCVS) Tumor Databases hereafter will be referred to as the databases. The HCVS system of databases is defined as the organized accumulation of information needed for the numerical subroutines to perform their functions. The databases all operate in the following manner. Based on input or instructions from the user module interfaces the connection module in the HCVS system will access databases, provide information to numerical solution modules and their subroutines to generate results and reports relevant to the human cancer virtual simulation under study. The databases described in this version are the DNA (genetic) database, biomarker (molecular) database, statistical database of information from actual patients, and a metastatic database.

Genetic Database

The DNA database includes information concerning genes of human cells as part of the carcinogenesis. The information will include cellular genes that are mutated and/or deleted. This information will include why, when, how, and other parameters of need for the simulation system's subroutines.

Molecular Database

The molecular database includes information that provides biochemical evidence of human carcinogenesis. This database will include human normal cell and cancer cellular molecular information, for example the phenotype of the mutated genes from the genetic database. This information will include biochemical mechanisms, protein functions and possible biological significant compounds.

Statistical Database

The statistical database includes information from studies performed for the specific forms of human cancer the engine is asked to examine. The statistical database will also include lifestyle issues related to specific cancers. This information is useful for all of the applications of the invention. Examples include information on the average age of a cancer patient at death, physiological information concerning the average size of an adenoma stage 1 tumor, etc.

Metastatic Database

The metastatic database includes all types of previously mentioned information specific to metastasis. This metastatic information will support the metastatic module of the HCVS.

System Overview and Operation

The invention is implemented on a computer, including an information input device, such as a keyboard, and a visual monitor or printer for output. The simulation system includes a series of software program modules each employing a system of specially written programs in conjunction with the above-described databases that utilizes a computer to perform its operations and generate results. These programs allow the user to enter individual patient information, if desired, or to use pre-programmed information producing information results in the form of reports about simulated human cancer. As shown in Fig. 1, the operator interface (including keyboard, mouse and display device in operative connection with a central processing unit) sends data and instructions to the engine, where they are processed, and processed data and instructions are sent by the engine back to the operator interface for output to the operator in the form of graphical displays, textual displays, or printed reports.

As illustrated by Fig. 2, the invention has two major configurations, educational and medical applications. The medical applications configuration allows diagnostic, treatment and research human cancer simulations to be performed. The educational configuration uses pre-programmed information, but allows limited interaction for the medical student's or training professional's educational purposes. The medical application configuration generates human cancer simulation information. This information can be in the form of reports of present information, and/or statistical and predictive information correlated to applicable time lines in the future or from the past. This configuration allows selection of modules and patient input to be entered into the engine selectively. Depending on the module selection, the user can move into the future or backward in time to generate simulated human cancer results. The system provides the capability to predict future courses of human cancer, and to describe the possible origin sight and initial biological traits of human cancer in a patient. The

result from the engine is virtual in that it produces simulated descriptions of human cancer in the body in the present, the past, and the future.

The biological process for a cell's transformation from a normal cell to a cancerous cell and then to metastatic activity is described within six modules in this invention. As shown in Fig. 3, each section (biological stage and view) is organized into a module. The six modules are the tumor origin, cellular, colony, tissue, tumor and metastatic modules. Each module contains one or more subroutines. These subroutines carry out smaller descriptive and mathematical processes needed to simulate human cancer biology. Each of the subroutines will produce results in forms needed by the user to describe the biological process the subroutine simulates. There are fourteen different subroutines within the system of the invention. The subroutines are as follows:

The *genetic mutation subroutine* and *diagnostic subroutine* of the tumor origin module,

The *cell cycle subroutine* and the *physical properties subroutine* of the cellular module,

The *interaction between cells subroutine* and the *structure subroutine* of the colony module,

The *interaction between cells subroutine* and the *tissue structure subroutine* of the tissue module,

The *interaction between cells subroutine*, the *tissue structure subroutine*, and *the physical properties of the tumor subroutine* of the tumor module, and

The *statistical and clinical outcome subroutine*, the *molecular biological subroutine*, and the *cancer origin/run forward subroutine* of the metastatic module.

The results are in the form of reports, generated by the subroutines of the modules, and placed into data sets. The data sets can then be viewed in the interface corresponding to the module that the reports came from.

As illustrated in Fig. 3, the invention has six module user interfaces, the molecular, cellular, cellular expansion, pre-neoplastic, neoplastic and metastatic interfaces. These interfaces each correspond to a respective module and act as information input and output points. This is where the human user receives instructions or requests, where choices about subroutines or their information output reports are chosen and where input information about a patient is entered to allow the programs to operate. It is at the user interface where the reports, that the subroutine generated and places into data sets, will be viewed. Thus the input information goes in through the user interfaces and the output information sets come back out of the user interface (see Fig 1).

A general example of the entire process that the simulation system uses is described in Fig 4. In operation, the user selects a particular module for operation. Each module and its subroutines then follows a process of operating the associated interface using the computer monitor and keyboard. The module then initiates activation of the central processing unit through the software programs with the connection module connecting the module to the databases of information needed for the subroutines. The modules then engage the numerical solutions module and the subroutines associated with the numerical solutions module and finally provide the user with reported solutions to user requests through the monitor and various other displays. All of the operations take place in the basic computer hardware and software previously described.

The connection module is activated whenever the input from the user is completed and the user initiates the subroutines. The connection module processes the input from the user, gathers information from the various databases necessary for the execution of the mathematical and descriptive algorithms within the various numerical solution modules and transmit it to its proper location. If the program is stopped at the user interface

along any aspect of the time line, and input is modified, the connection module will automatically engage to transmit to the numerical solutions module the new information. The numerical solutions module will then generate the sequential processing. If the program is paused, the connector module will disengage. The numerical solutions module subroutines carry out the task of generating the results for the reports. Once started they will generate the previously mentioned results and arrange them into reports. These reports will be sent to the user interface for viewing on the monitor or for printing. If continual output is chosen and the user stops the program, the numerical module (s) will store results generated up to that point in time. The user may at any time request reports. If the program is restarted it will begin where it left off, include the changed parameters in the next sequential report, continue calculations with modified parameters and produce a new report. If paused, the numerical module will resume its calculations when the pause is ended, generate its results, report back to the user interface and the process is completed.

Detailed descriptions of the various subroutines of each module will now be described with reference to Figs. 5-10.

TUMOR ORIGIN MODULE

Referring to Fig. 5, the HCVS Tumor Origin Module has two purposes. The first purpose is to use mathematical calculations to go back in time to the original site of carcinogenesis. This will include the original genetic mutations found to be the initiatory step of the disease. The initiatory step is the first mutation of a normal cell that leads to the phenotype of the specified cancer.

The second purpose of the Tumor Origin Module is to diagnose cancer at the genetic level. This will be the cutting edge of the early detection technology. For example, in colon cancer there are set genetic steps to carcinogenicity. If the patient had a biopsy of a benign polyp and the molecular (i.e. genetic) information was extracted, it could be entered into the HCVS and the Tumor Origin Module would diagnose the probability of a future malignancy.

The operator enters information about the patient and their current tumor into the system through the operator interface. This will include the age, weight, and other relevant physiological information about the patient. This information is then run through the tumor origin subroutines in the Tumor Origin Module. This information will then result in a report(s) of information about the location and molecular properties of the tumor's origin.

Prostate cancer is a good example of the function of this module. In prostate cancer the disease's initiatory step is not fully understood. The main reason for the complexity of prostate cancer is the heterogenicity of the tumors. In the prostate there are several primary tumors at detection. Within the detected prostate tumors there are several different genotypes. This complexity makes early detection of prostate cancer for a pathologist difficult. The tumor origin module of the HCVS will be able to trace the tumors' progress from the state of the detected tumor back in time using the databases and calculations of the subroutines. The product of the subroutine executions will be molecular information showing the probability of which mutation or series of mutations could be the initiatory step.

The display of the resultant information is described in the molecular interface.

Genetic Mutation Subroutine of the Tumor Origin Module

The purpose of the genetic subroutine of the tumor origin module is to calculate the different mutations that can occur in cellular genetic code involving cell transformation steps leading to, and resulting in, a cancerous state. The genetic mutations can occur by three different methods (deletion, insertion, and substitution) these three methods lead to codon mutations (chain termination mutation, frameshift mutation, missence mutation, and nonsense mutations). Other somatic mutations also exist, these mutations only occur in somatic cells. By the pathways of mutation being limited we can categorize a mutation to have a specific phenotype. The genetic mutation will then effect the cell by the expression or non-expression of the gene's protein.

For example, in order to inactivate the APC (Adenmatous Polyposis Coli) gene both alleles must be lost. In the situation of Familial Adenomatous Polyposis Syndrome a recessive APC allele is inherited. At this point only one mutation (i.e. a somatic mutation) needs to occur in order to lose APC function. (See Human Cancer Virtual Simulation Cellular Module to see the results of an APC deletion) By simulating these relationships, the tumor origin module will be able to examine the existing situation (disease) and estimate back to the tumors origin. These genetic mutations and functional relationships will be mathematically operated in the genetic subroutine of the origin module.

Diagnosis from Molecular Information Subroutine of the Tumor Origin Module

The purpose of the diagnosis from the molecular information subroutine in the tumor origin module is to improve early detection of cancer. For example, in colon cancer, the accepted initiatory step is the mutation of APC. If, as described earlier, a user had the molecular information for a benign polyp of a patient and this information was entered into the HCVS the diagnosis from molecular information subroutine would calculate the probable timing and initial intensity of a future malignancy.

Tumor Origin Module Information Sets

Both of the tumor origin module subroutines, genetic mutation and diagnosis from molecular information will have information outputs that will be inputted into the molecular interface.

Genetic Mutation Subroutine

•The type and location of the genetic mutation.

Using the information from the genetic database the genetic mutation subroutine will show the type and location of the genetic mutation that has occurred.

•The phenotypic result of the genetic mutation.

Using the genetic database as well as the molecular database the genetic mutation subroutine will express the phenotypic results of the mutated genes. This will include protein expression, protein reactions, and etc.

•The gene products lost in the mutation.

Using the molecular database the genetic mutation subroutine will determine the gene products that are

lost due to the genetic mutation. The operator will be able to activate and deactivate genes therefore effecting the gene products. This information will then be available to the operator to view and manipulate.

Diagnosis from Molecular Information Subroutine

•The possible initiatory step and the probability it has occurred

Using the genetic and the molecular databases, the diagnosis from molecular information subroutine will calculate a list of possible initiatory steps and their probability. This information will be displayed on the molecular interface, and the operator will be able to manipulate the scenarios using this interface.

•The mutations that have occurred and follow the carcinogenic path and the mutations along that same path that have not occurred.

Using the genetic and the molecular databases, the diagnosis from molecular information subroutine will determine the most likely genetic pathway. From the most probable carcinogenic pathway, the diagnosis from molecular information subroutine will determine the genetic variations that have occurred, and the genetic variations that will occur, if the selected pathway is followed.

•The probability and proposed carcinogenic pathway.

Using the genetic and molecular databases, the diagnosis from molecular information subroutine will determine all the possible carcinogenic pathways and their corresponding probability. This information will be displayed and the operator will be able to select a pathway and the engine will analyze it.

Molecular Interface

The molecular interface will display and allow user interaction with the module for the information on the actual interaction of the genes and molecules. The reports will include chemical mechanisms, bond strengths, timing of mutations, possible alternative mutations, etc.

The cell bonding strength is an example of the information included in the molecular level. In the cell bonding the APC product must undergo homo-oligomerization to produce the beta-catenin that is essential for the production of the cell bonding cadherin. In the situation where an APC deletion would occur, the cell bond strength would be reduced. The information will be available concerning the reaction mechanism, time of reaction, conditions of reaction, and etc.

CELLULAR MODULE

As shown in Fig. 6, the Cellular Module is the portion of the HCVS engine that controls the cellular information. The purpose of the Cellular Module is to use mathematical calculations to describe the behavior of an individual cell and its surrounding environment. The Cellular Module will accomplish its tasks by mathematically calculating the properties of the cells. This is described in the subroutines of this module.

The control of an individual cell and it's environment is shown by an example of p53 gene loss. The

p53 gene is a tumor suppressor gene. The p53 gene activates the p21 protein. The p21 protein has the function of arresting cell cycle progression so the cell can either undergo repair or apoptosis. This is accomplished by inhibiting cyclin cdk complexes. When p53 is mutated the p21 protein doesn't activate at the levels necessary and the cell continues through a complete cycle to produce two mutated daughter cells. This process, and many others not described, are part of carcinogenesis, and will be controlled through said mathematical calculations in the cellular module.

The display of the resultant information is described in the cellular level interface.

Cell Cycle Subroutine of the Cellular Module

The purpose of the cell cycle subroutine of the cellular module is to simulate the aspects of a cell life cycle. These aspects will include the timing of the cell cycle, control of the stage of the cell cycle, etc. The required information will be in the molecular database. The cell cycle subroutine will use statistical and chemical information to run its calculations.

The control of the cells cycle properties is shown in the p53 example (see Cellular Module). The effects of the mutation of the p53 gene will affect the timing of mitosis. This effect is an increase in speed because the cell doesn't stop the process of cell cycle progression to repair the mutation.

Physical Properties of the Cell Subroutine of the Cellular Module

The purpose of the physical properties of the cell subroutine of the cellular module is to describe mathematically the size, shape and structure of the cell changes throughout carcinogenesis. For example, in the shape of the cells in large cell undifferentiated carcinoma there is a classification of cells named clear cell. This nomenclature came about due to the cytoplasm of a cell turning clear during carcinogenesis. This state occurs because of large deposits of glycogen in the cytoplasm.

Cellular Module Information Sets

Both of the cellular module subroutines, cell cycle and physical properties of the cell will generate information from its calculations and return this information to the cellular level interface.

<u>Cell Cycle Subroutine</u>

•Rate of mitosis

Using the molecular and the statistical databases the cell cycle database will produce information on the rate of mitosis in the form of time/cell cycle. This information will be useful in determining the speed of the diseases' progression. The operator will be able to adjust the cycle in order to view hypothetical situations, but the system will always default back to the calculated "real life" rate.

•Survival rate of the cells

Using the molecular and statistical database the cell cycle subroutine will determine the mean and standard deviation/time of the survival rates of cells. This subroutine will also determine the number of cells that induce apoptosis as a normal function. As described in the cellular module many mutated cells will induce

apoptosis to deter a genotype or phenotypic mutation from progressing. In carcinogenesis one of the factors is the situation that the gene products that are responsible for apoptosis are themselves mutated. This information will be displayed in the cellular level interface.

Physical Properties of the Cell Subroutine

•Physical properties of the cell.

Using the molecular and statistical databases the physical properties of the cell subroutine will determine the size, shape, physical makeup, and etc. This information will be displayed on the cellular level interface and will be used as information by other modules.

Cellular Interface

The cellular level of information will display the rate of mitosis, the rate and level of mutation, the size and shape of the cell, etc. generated by the Cellular Module of the HCVS engine. The rate of mitosis is an example of important information at the cellular level. The HCVS will be able to give the information concerning the shape size and rate of replication (mitosis). The time and stage of the disease will reference this information from the cell. The operator will be able to select the information set according to time to see the size and shape of the cells at various times in the past, present or future. The other variables will be available for adjustment as well. The operator will have tailored the HCVS for the specific case and will then enter the size and shape of the cells they are looking at. The operator will then enter that information and the HCVS will generate the information for the probable time and stage of the disease.

COLONY MODULE

Referring to Fig. 7, the purpose of the Colony Module is to mathematically describe small cellular populations. The importance of this can be shown by nutrition consumption: When a pre-neoplastic growth occurs, the nutrition consumption of the growth increases from its standard rate of consumption. This happens for many reasons, but an example is cellular growth rate. The pre-neoplastic growth occurred partly because of an increased growth rate. This increased growth rate needs more nutrition from the body. This imbalance will lead to the cells around the growth to give up some of their needed nutrition to the growth; the colony module through mathematical calculations will determine this dynamic relationship.

The display of the resultant information is described in the cellular expansion interface.

Interaction between Cells Subroutine of the Colony Module

The purpose of the interaction between cells subroutine of the colony module is to control the interaction of simulated cells through mathematical calculations. The nutritional consumption described in the colony module is good example of this relationship. Other modules in the invention will use the information from this subroutine.

Structure Subroutine of the Colony Module

The purpose of the structure subroutine of the colony module is to show the structure of the cells together in this small population. The structure subroutine will include the physical characteristics of the individual cells but will also include the structural relationship of the cells together. In large cell undifferentiated carcinoma of the lung, the physical properties of the cell along with this intracellular structure are the keys to diagnosis and classification.

Colony Module Information Sets

Both of the subroutines of the colony module, interaction between cells and structure, will produce information and return it to the cellular expansion interface.

Interaction between Cells Subroutine

•Nutrition Consumption

Using the molecular and statistical databases, the interaction between cells subroutine will produce information in the measurement of moles/unit. This information will include all standard compounds that are biochemically necessary, but also will include a section to input a new compound along with its chemical properties and the interaction between cells subroutine will calculate the involvement.

•Cell Bonding

Using the molecular database the interaction between cells subroutine will calculate the bond strength between cells. Some of the contemplated modes of measurement are kcal/mol necessary to break the bond and etc. This information will be displayed on the cellular expansion interface, but will also go into the information input area to fuel other modules.

Structure Subroutine

•Physical Properties of the Individual Cells

Using the molecular and statistical databases the physical properties of the cell subroutine will determine the size, shape, physical makeup, and etc. This information will be displayed on the cellular level interface and will be used as information by other modules.

•Intracellular Structure

Using the molecular and statistical database the structure subroutine will produce information for the structure of the tissue. This structure will take on many forms and functions. This information will be displayed on the cellular expansion interface.

Cellular Expansion Interface

The cellular expansion interface will be where the information form the subroutines of the Colony Module (concerning small populations of cells and their interactions) will be shown and described to the user.

The operator will be able to adjust the variables such as oxygen distribution in order to see the interaction between the simulated cells described by the subroutine programs. The value of the information displayed here to the user is that these relationships would be difficult to see in the later interfaces.

TISSUE MODULE

Referring to Fig. 8, the purpose of the Tissue Module is to describe with mathematical calculations a large population of different cells interacting in a normal and a malignant environment. Within the tissue of every organ there are several different types of cells. The different types of cells have different functions and therefore different locations. The Tissue Module will describe small abnormal growths. The interactions between the small growth and the outer levels of the tissue, are important to describing and understanding the path of carcinogenesis in practical terms. These interactions are described mathematically by the tissue module.

The display of the resultant information is described in the pre-neoplastic interface.

Interaction between Cells Subroutine of the Tissue Module

The purpose of the interaction between cells subroutine of the tissue module is to mathematically describe the intracellular interaction among large populations of simulated cells within the Tissue Module. The nutritional consumption described in the Colony Module is a good example of this relationship. Other modules in the invention will use the information from this subroutine.

Tissue Structure Subroutine of the Tissue Module

The purpose of the tissue structure subroutine of the Tissue Module is to mathematically control the intracellular structure among large populations of simulated cells within the Tissue Module. As described in the Structure Subroutine of the Colony Module, the structure of the intracellular relationship is important not only in diagnosis but in cellular classification. In the Tissue Module, this subroutine will also begin to generate the different layers of the tissue cross section. In all tissues there are several levels of tissue within the tissue sample. This subroutine will generate the information needed to represent these levels and their interaction with each other.

Tissue Module Information Set

Both of the subroutines of the tissue module, interaction between cells and tissue structure, will produce information and return it to the pre-neoplastic interface.

Interaction between Cells Subroutine

•Nutrition Consumption

Using the molecular and statistical databases, this subroutine will produce information in the measurement of tissue level nutritional consumption. The simulation will generate information in chemical terms (i.e. moles) relevant to the user. The unit may vary dependent on the organ simulation. This information will include all standard compounds that are biochemically necessary, but also will include a section to input a new

compound along with its chemical properties and the interaction between cells subroutine. The subroutine will then calculate the chemical interaction of the new compounds at the tissue level and display the information at the pre-neoplastic interface.

•Cell Bonding

Using the molecular database the interaction between cells subroutine will calculate the bond strength between simulated cells in the tissue module. One of the contemplated modes of measurement are kcal/mol necessary to break the bond among others not described. This information will be displayed on the pre-neoplastic interface, but will also go into the information input area to fuel other modules.

Tissue Structure Subroutine

•Physical Properties of the Individual Cells

Using the molecular and statistical databases the physical properties of the cell subroutine will determine the size, shape, physical makeup, and etc. of the simulated cells within the tissue module. This information will be displayed on the pre-neoplastic interface and will be used as information by other modules.

•Intracellular Structure

Using the molecular and statistical database the structure subroutine will produce information for the structure of the simulated tissue. This structure will take on many forms and functions. This information will be displayed on the pre-neoplastic interface

•Tissue Levels

Using the molecular and statistical database the tissue structure subroutine will generate information concerning the development, size, shape, and etc. of the tissue. This information will be presented on the pre-neoplastic interface.

Pre-neoplastic Interface

The pre-neoplastic interface will display information from the Tissue Module information set, such as nutritional consumption and the other information sets described which are generated by the Tissue Module subroutines. This level will show information from the earliest stages of a simulated primary tumor or tumors. This information will also be available for the operator to manipulate as in the previous levels.

TUMOR MODULE

Referring to Fig. 9, the purpose of the Tumor Module is to control complex relationships of simulated tumor growth through mathematical calculations for the majority of tumorigenesis. This process needs its own module because of the complexity of the interactions between the disease and the surrounding cells.

The development of blood vessels is a good example of the complexity of the systems of the Tumor Module. The primary tumor will continue to grow at an accelerated rate as long as the nutrients are available for

the growth. (When the threshold is reached where the nutrients are limited, this corresponds to the weak cell bonds discussed earlier.) This weakness allows for the nutrient carrying blood to reach the tumor and form small blood vessels. This relationship, along with many others, will be controlled mathematically by the Tumor Module.

The display of the resultant information is described in the neoplastic interface.

Interaction between Cells Subroutine of the Tumor Module

The purpose of the interaction between cells subroutine of the Tissue Module is to mathematically run the intracellular interaction. The nutritional consumption described in the Colony Module is a good example of this relationship. Other modules in the invention will use the information from this subroutine.

Tissue Structure Subroutine of the Tumor Module

The purpose of the tissue structure subroutine of the Tumor Module is to mathematically control the intracellular structure. As described in the Structure Subroutine of the Colony Module, the structure of the intracellular relationship important not only in diagnosis but in classification. In the Tissue Module this subroutine will also begin to generate the different layers of the tissue cross section. As in all tissues there are several levels of tissue with in the tissue sample. This subroutine will generate the information needed to represent these levels and their interaction with each other.

Physical Properties of the Tumor Subroutine of the Tumor Module

The purpose of the physical properties of the tumor subroutine of the Tumor Module is to calculate the behavior of the virtual disease. This subroutine will handle information such as tumor mass, growth rate, cell structure, etc. The information describing that characteristic will be generated in the physical properties of the tumor subroutine.

An example of the physical properties of a tumor is prostate cancer, as mentioned previously (see Tumor Origin Module) where there are multiple primary tumors.

Tumor Module Information Sets

Each of the three subroutines; interaction between cells, tissue structure, and physical properties of the tumor subroutine, will generate information for the neoplastic interface. The first two subsections have already been described and are referenced. The last of the three subroutines' results is described below.

Physical Properties of the Tumor

•Tumor Mass

The physical properties of the tumor will describe the size, shape, and overall mass of the primary tumor. This information will be shown in a metric scale and percentage of total area. This information will also be sent to the input information area to help run other modules.

•Tumor Growth Rate

The physical properties of the tumor, generate tumor growth information concerning the growth of a tumor over time. This information will also include the major factors driving the growth. This will be sent to the input information area, as was the tumor mass information.

•Genetic Mutations Present

Using all the databases except the metastatic database, the physical properties of the tumor subroutine will determine the genetic changes that have occurred and will occur during the simulation.

•Vascular Construction

Using the molecular and statistical database the physical properties of the tumor database will generate information for concerning vascular construction. This information will also come from the tissue module. This information will be sent to the information-input area to help run the metastatic module.

Neoplastic Interface

The neoplastic interface will display the information from the Tumor Module. The complex relationships will be shown and available for adjustment. This interface will show the most information concerning the primary growth.

After entering all the information concerning the patient and the disease, the operator will then be able to adjust the size of the tumor to determine the stage that the patient is in. The operator will also be able to adjust the information to see the corresponding information, the order of mutations that have occurred and see the information for the mutations that have yet to occur.

METASTATIC MODULE

Referring to Fig. 10, the Metastatic Module is a human cancer predictive and prognostic engine used to simulate and generate simulations and reports about cancer behavior in the human body. It uses information supplied to its various subroutine computer software programs or using pre-programmed instructions to accomplish this. The purpose of the Metastatic Module is to provide useful information from mathematical and descriptive algorithms to help forecast and predict the course of cancer progression in the human body.

A second use of the module is to examine the possible effects of treatment intervention steps using input supplied to its programs. The input supplied to the programs within the Metastatic Module may be specific to an individual or the program can examine possible futures based on assumptions within the program. This module has significant diagnostic and therapeutic applications for human cancer patients and the physicians that treat them. Due to the importance of this module and the predictive and prognostic applications, its operation will be described in more detail and serve as a fuller example of what the invention is intended to do.

The Metastatic Module Subroutines, Their Scientific Assumptions and Mode of Operation

There are three metastatic cancer predictive and prognostic subroutines that appear on the user interface

once the Metastatic Model is selected. The first would be a clinical and statistical outcome, the second would be molecular biological, and the third would be cancer origin/run forward.

The Statistical and Clinical Outcome Subroutine of the Metastatic Module

The Statistical and Clinical Outcome subroutine will use epidemiological information (morbidity, mortality, height, weight, treatment steps such as chemotherapy, surgery and radiation; when treatments were administered, patient response to treatment or estimates thereof, initial tumor size and volume, tumor geometric shape, tumor location, patient age, health conditions of relevance to patient such as HIV status, immune system strength through secondary biomarkers such as white blood cell and T-cell count, family history of relevance to cancer epidemiology, other complicating factors or diseases, local and distant metastases location, biomarkers of human cancer such as estrogen receptivity in breast cancer and others, mitosis rate, cell diploidy, etc.) assembled into databases previously described within the invention and gathered from credible scientific sources from real human cancer patients relating to the course of human cancer. The purpose and resulting information from this subroutine is to predict the future course of a patient's human cancer by relating user inputted information related to the database described and using linear mathematics within the subroutine coupled with inputted information and assumptions to predict possible clinical disease outcomes for the patient/physician. The underlying assumption is that future cancer behavior will be similar to that documented from the past and the engine information will prove useful for predictive and prognostic purpose.

Molecular Biological Subroutine of the Metastatic Module

The molecular biological subroutine will use information known about a cancer or tumor (pathology report information such as tumor size and volume, tumor geometric shape, type of cancer, tumor location, level of vascularity within the tumor, location to veins and artery in target organ, mitosis rate, biomarkers of relevance, cell differentiation, cell diploidy etc.) in addition to patient characteristics of importance to the engine (height, weight, treatment steps such as chemotherapy, surgery and radiation; when treatments were administered, patient response to treatment or estimates thereof, patient age, health conditions of relevance to patient such as HIV status, immune system strength through secondary biomarkers such as white blood cell and T-cell count, family history of relevance to cancer epidemiology, other complicating factors or diseases, local and distant metastases location, etc.) and generate information related to micro metastasis rate and behavior of cancer cells or emboli (clusters of cancer cells) and their ability to move to new sites developing possible and probable scenarios of human cancer reoccurrence and growth within the body. The underlying assumption in this subroutine is to provide populations of individual cells with instructions, based on what is known about the patient and their cancer's molecular biological behavior, that will influence cancer cell growth, death, and other disease characteristics within the body. The molecular biological subroutine will then begin functioning, using programs and assumptions inputted by the physician about a patient to provide information useful for prognosis and prediction of human cancer.

Cancer Origin/Run Forward Subroutine of the Metastatic Module

The cancer origin/run forward subroutine is a sequential operation of the Cancer Origin module which will be a reverse operation of the subroutines within the tumor, tissue, colony, cellular and finally tumor origin modules and then followed by the molecular biological subroutine. The underlying assumption of the cancer origin module is beginning at a point in time when the cancerous tumor is discovered a simulation with the HCVS engine can be developed running backward in time using the various modules to reach the origin of cancer development. The HCVS engine can then be run forward through the present and into the future. It is envisioned this will provide useful information for prognosis and prediction of human cancer behavior. One advantage of the cancer origin/run forward subroutine is that it can test engine input for efficacy. When information from this subroutine generates information that closely resembles the patient's disease condition in the present, that result may be used to decide parameters to drive simulations in the future. Additional information that could be provided by using this technique would be additional micro metastasis not seen at the primary site of the tumor.

Metastatic Module Information Set

Each of the three Metastatic Module subroutines, statistical and clinical outcome , molecular biological and cancer origin/run forward will contain numerical solution modules to perform the following estimations and descriptions and generate reports back to the user interface and can be selected by the user: a) metastatic occurrence, target organ and percentage possibility, b) percentage disease free survival, c) micro metastatic and metastases volume, d) projected cancer cellular mitosis phase table, e) projected blood biomarker concentration over time.

Considering now that the system herein described will have 15 different numerical solution modules described in the diagram for this part of the invention in greater detail, each numerical solution module within the 3 Metastatic Module subroutines will be described as to what it will do beyond the general function of a numerical solution module above and how it will perform its said function:

<u>The Statistical and Clinical Outcome Numerical Solution Module Output Subroutines</u>

•Metastatic occurrence, target organ and percentage possibility.

Using information from the epidemiological database and from other databases within the invention an algorithm will be constructed that will make use of medical and personal input about an individual patient's present condition to determine the probable organ sites of distant metastatic human cancer projected in a future time frame. The algorithms will use linear and curvilinear analysis and other mathematical means to achieve this endpoint. Where possible the algorithm will use statistical analysis to determine the confidence of its predictions.

•Percentage disease free survival

Using information from the epidemiological database and from other databases within the invention, an algorithm will be constructed that will make use of medical and personal input about an individual patient's present condition to determine the morbidity and mortality of distant metastatic human, cancer projected in a

future time frame to generate predictions of disease free survival. The algorithms will use linear and curvilinear analysis and other mathematical means to achieve this endpoint. Where possible, the algorithm will use statistical analysis to determine the confidence of its predictions.

•Micro metastatic and metastases volume

Using information from the epidemiological database and from other databases within the invention an algorithm will be constructed that will make use of medical and personal input about an individual patient's present condition to determine the micro metastatic and metastases volume of distant metastatic human cancer projected in a future time frame. The algorithms will use linear and curvilinear analysis and other mathematical means to achieve this endpoint. It is envisioned that this description will encompass assumptions about micro metastatic behavior not visibly seen but that can be inferred from the scientific literature. Where possible, the algorithm will use statistical analysis to determine the confidence of its predictions.

•Projected cancer cellular mitosis phase table

Using information from the epidemiological database and from other databases within the invention, an algorithm will be constructed that will make use of medical and personal input about an individual patient's present condition to determine the projected cancer cellular mitosis phase table of metastatic human cancer, projected in a future time frame to generate predictions about cancer cell populations and their behavior. It is expected that this program will generate information about cellular functions of interest, such as S-phase, mitosis or m-phase doubling rate and many others to be specified. The algorithms will use linear and curvilinear analysis and other mathematical means to achieve this endpoint. Where possible the algorithm will use statistical analysis to determine the confidence of its predictions.

•Projected blood biomarker concentration over time.

Using information from the epidemiological database and from other databases within the invention an algorithm will be constructed that will make use of medical and personal input about an individual patient's present condition to determine the projected blood biomarker concentration over time of metastatic human cancer projected in a future time frame. It is expected that this program will generate information about chemical behavior of cancer cells, including biomarkers but not limited to them, chemical metabolic factors associated with cancer may be included. It is envisioned that numerical solution program will be mathematically linked to predictions generated by the micro metastatic and metastases volume, projected cancer cellular mitosis phase table and the metastatic occurrence, target organ and percentage numerical module subroutines, or their predictions, within this module. These numerical solution modules will probably include mathematical expression to determine uptake by various organs in the body and other mathematical modeling expressions to provide a close to reality prediction of the concentration of chemicals of interest in the bloodstream. The algorithms will use linear and curvilinear analysis and other mathematical means to achieve this endpoint. Where possible, the algorithm will use statistical analysis to determine the confidence of its predictions.

Molecular Biological Numerical Solution Module Output Subroutines

•Metastatic occurrence, target organ and percentage possibility

Using information from the GENETIC database and from other databases within the invention an algorithm will be constructed that will make use of medical and personal input about an individual patient's present condition to determine the probable organ sites of distant metastatic human cancer projected in a future time frame. The algorithms will use linear, curvilinear, geometric, algebraic functions and other mathematical means to achieve this endpoint. The algorithm (s) within this numerical solution module will extend and improve upon the mathematical expressions of the HCVS engine modules that will simulate genetic changes of a cell to cancerous tumor and cellular overgrowth to include descriptions of breakout or micro metastatic shed rate, new blood vessel formation; blood, tissue and lymph vessel invasion, survival in the bloodstream, tissue transport and new colony formation at secondary or tertiary sites. It is envisioned that information useful for motion, shape, path and particle behavior of cancer in the body will be generated. Where possible, the algorithm will use statistical analysis to determine the confidence of its predictions.

•Percentage disease free survival.

Using information from the GENETIC database and from other databases within the invention an algorithm will be constructed that will make use of medical and personal input about an individual patient's present condition to determine the percentage of disease free survival from distant metastatic human cancer projected in a future time frame. The algorithms will use linear, curvilinear, geometric, algebraic functions and other mathematical means to achieve this endpoint. The algorithm (s) within this numerical solution module will extend and improve upon the mathematical expressions of the HCVS engine modules that will simulate genetic changes of a cell to cancerous tumor and cellular overgrowth to include descriptions of breakout or micro metastatic shed rate, new blood vessel formation; blood, tissue and lymph vessel invasion, survival in the bloodstream, tissue transport and new colony formation at secondary or tertiary sites. It is envisioned that information useful for motion, shape, path and particle behavior of cancer in the body will be generated. Where possible, the algorithm will use statistical analysis to determine the confidence of its predictions.

•Micro metastatic and metastases volume

Using information from the GENETIC database and from other databases within the invention an algorithm will be constructed that will make use of medical and personal input about an individual patient's present condition to determine the micro metastatic and metastases volume of distant metastatic human cancer projected in a future time frame. The algorithms will use linear, curvilinear, geometric, algebraic functions and other mathematical means to achieve this endpoint. The algorithm (s) within this numerical solution module will extend and improve upon the mathematical expressions of the HCVS engine modules that will simulate genetic changes of a cell to cancerous tumor and cellular overgrowth to include descriptions of breakout or micro metastatic shed rate, new blood vessel formation; blood, tissue and lymph vessel invasion, survival in the bloodstream, tissue transport and new colony formation at secondary or tertiary sites. It is envisioned that information useful for motion, shape, path and particle behavior of cancer in the body will be generated. Where

possible, the algorithm will use statistical analysis to determine the confidence of its predictions.

•Projected cancer cellular mitosis phase table.

Using information from the genetic database and from other databases within the invention an algorithm will be constructed that will make use of medical and personal input about an individual patient's present condition to determine the projected cancer cellular mitosis phase table of distant metastatic human cancer projected in a future time frame. The algorithms will use linear, curvilinear, geometric, algebraic functions and other mathematical means to achieve this endpoint. The algorithm (s) within this numerical solution module will extend and improve upon the mathematical expressions of the HCVS engine modules that will simulate genetic changes of a cell to cancerous tumor and cellular overgrowth to include descriptions of breakout or micro metastatic shed rate, new blood vessel formation; blood, tissue and lymph vessel invasion, survival in the bloodstream, tissue transport and new colony formation at secondary or tertiary sites. It is envisioned that information useful for motion, shape, path and particle behavior of cancer in the body will be generated. Where possible, the algorithm will use statistical analysis to determine the confidence of its predictions.

• Projected blood biomarker concentration over time.

Using information from the genetic database and from other databases within the invention, an algorithm will be constructed that will make use of medical and personal input about an individual patient's present condition to determine the projected blood biomarker concentration, over time, of distant metastatic human cancer projected in a future time frame. The algorithms will use linear, curvilinear, geometric, algebraic functions and other mathematical means to achieve this endpoint. The algorithm (s) within this numerical solution module will extend and improve upon the mathematical expressions of the HCVS engine modules that will simulate genetic changes of a cell to cancerous tumor and cellular overgrowth to include descriptions of breakout or micro metastatic shed rate, new blood vessel formation; blood, tissue and lymph vessel invasion, survival in the bloodstream, tissue transport and new colony formation at secondary or tertiary sites. It is expected that this program will generate information about chemical behavior of cancer cells, including biomarkers, but not limited to them. Chemical metabolic factors associated with cancer may be included. It is envisioned that numerical solution program will be mathematically linked to predictions generate by the micro metastatic and metastases volume, projected cancer cellular mitosis phase table and the metastatic occurrence, target organ and percentage numerical module subroutines, or their predictions, within this module. This numerical solution module will probably include mathematical expressions to determine uptake by various organs in the body and other mathematical modeling expressions to provide a close to reality prediction of the concentration of chemicals of interest in the bloodstream. Where possible, the algorithm will use statistical analysis to determine the confidence of its predictions.

<u>Cancer Origin/Run Forward Numerical Solution Module Output Subroutines</u>

•Metastatic occurrence, target organ and percentage possibility

Using information from the genetic database, the molecular database and from other databases within the

invention, an algorithm will be constructed that will make use of medical and personal input about an individual patient's present condition to determine the probable organ sites of distant metastatic human cancer projected in a future time frame. The algorithm will reverse the process to the origin of cancer and then move forward through the present to future time frames. The algorithms will use linear, curvilinear, geometric, algebraic functions and other mathematical means to achieve this endpoint. The algorithm (s) within this numerical solution module will extend and improve upon the mathematical expressions of the Cancer Origin and HCVS engine modules that will simulate genetic changes of a cell to cancerous tumor and cellular overgrowth to include descriptions of breakout or micro metastatic shed rate, new blood vessel formation; blood, tissue and lymph vessel invasion, survival in the bloodstream, tissue transport and new colony formation at secondary or tertiary sites. It is envisioned that information useful for motion, shape, path and particle behavior of cancer in the body will be generated. Where possible, the algorithm will use statistical analysis to determine the confidence of its predictions.

•Percentage disease free survival

Using information from the cancer origin database, the molecular database and from other databases within the invention, an algorithm will be constructed that will make use of medical and personal input about an individual patient's present condition to determine the percentage of disease free survival from distant metastatic human cancer projected in a future time frame. The algorithm will reverse the process to the origin of cancer and then move forward through the present to future time frames. The algorithms will use linear, curvilinear, geometric, algebraic functions and other mathematical means to achieve this endpoint. The algorithm (s) within this numerical solution module will extend and improve upon the mathematical expressions of the cellular module to the tumor module that will simulate genetic changes of a cell to cancerous tumor and cellular overgrowth to include descriptions of breakout or micro metastatic shed rate, new blood vessel formation; blood, tissue and lymph vessel invasion, survival in the bloodstream, tissue transport and new colony formation at secondary or tertiary sites. It is envisioned that information useful for motion, shape, path and particle behavior of cancer in the body will be generated. Where possible, the algorithm will use statistical analysis to determine the confidence of its predictions.

•Micro metastatic and metastases volume

Using information from the cancer origin, the genetic database and from other databases within the invention, an algorithm will be constructed that will make use of medical and personal input about an individual patient's present condition to determine the micro metastatic and metastases volume of distant metastatic human cancer projected in a future time frame. The algorithm will reverse the process to the origin of cancer and then move forward through the present to future time frames. The algorithms will use linear, curvilinear, geometric, algebraic functions and other mathematical means to achieve this endpoint. The algorithm (s) within this numerical solution module will extend and improve upon the mathematical expressions of the Cancer Origin and HCVS engine modules that will simulate genetic changes of a cell to cancerous tumor and cellular overgrowth to include descriptions of breakout or micro metastatic shed rate, new blood vessel formation; blood, tissue and lymph vessel invasion, survival in the bloodstream, tissue transport and new colony formation at secondary or

tertiary sites. It is envisioned that information useful for motion, shape, path and particle behavior of cancer in the body will be generated. Where possible, the algorithm will use statistical analysis to determine the confidence of its predictions.

•Projected cancer cellular mitosis phase table

Using information from the cancer origin, the statistical and metastatic database and from other databases within the invention, an algorithm will be constructed that will make use of medical and personal input about an individual patient's present condition to determine the probable organ sites of distant metastatic human cancer projected in a future time frame. The algorithm will reverse the process to the origin of cancer and then move forward through the present to future time frames. The algorithms will use linear, curvilinear, geometric, algebraic functions and other mathematical means to achieve this endpoint. The algorithm (s) within this numerical solution module will extend and improve upon the mathematical expressions of the Cancer Origin and HCVS engine modules that will simulate genetic changes of a cell to cancerous tumor and cellular overgrowth to include descriptions of breakout or micro metastatic shed rate, new blood vessel formation; blood, tissue and lymph vessel invasion, survival in the bloodstream, tissue transport and new colony formation at secondary or tertiary sites. It is envisioned that information useful for motion, shape, path and particle behavior of cancer in the body will be generated. Where possible, the algorithm will use statistical analysis to determine the confidence of its predictions.

•Projected blood biomarker concentration over time.

Using information from the cancer origin, the statistical and metastatic database and from other databases within the invention, an algorithm will be constructed that will make use of medical and personal input about an individual patient's present condition to determine the projected blood biomarker concentration over time of distant metastatic human cancer projected in a future time frame. The algorithm will reverse the process to the origin of cancer and then move forward through the present to future time frames. The algorithms will use linear, curvilinear, geometric, algebraic functions and other mathematical means to achieve this endpoint. The algorithm (s) within this numerical solution module will extend and improve upon the mathematical expressions of the HCVS engine modules that will simulate genetic changes of a cell to cancerous tumor and cellular overgrowth to include descriptions of breakout or micro metastatic shed rate, new blood vessel formation; blood, tissue and lymph vessel invasion, survival in the bloodstream, tissue transport and new colony formation at secondary or tertiary sites. It is expected that this program will generate information about chemical behavior of cancer cells, including biomarkers but not limited to them. Chemical metabolic factors associated with cancer may be included. It is envisioned that numerical solution program will be mathematically linked to predictions generate by the micro metastatic and metastases volume, projected cancer cellular mitosis phase table and the metastatic occurrence, target organ and percentage numerical module subroutines, or their predictions, within this module. This numerical solution module will probably include mathematical expressions to determine uptake by various organs in the body and other mathematical modeling expressions to provide a close to reality prediction of the concentration of chemicals of interest in the bloodstream. Where possible the algorithm will use statistical

analysis to determine the confidence of its predictions.

Metastatic Interface

In operation, the Metastatic Module and its subprograms follow the system described in this invention of engaging a user interface using a standard computer monitor and keyboard. The Metastatic Module then activates the central processing unit through the software programs with the connector module connecting to databases of information needed for the numerical and descriptive processing. The Metastatic Module then engages the numerical solution module and subroutines and finally provides the user with reported solutions to their requests through the monitor and various displays. All of the operations take place in the basic software described in figure 3-10.

Similar to other modules described in this invention, the first phase of the Metastatic Module involves a fact gathering process for information input and the selection of programs and patient information to be entered to enable operation of the subprograms selected through a keyboard. Assuming the software is loaded and operational through conventional means, the user will be prompted to select modules of operation. When the Metastatic Module is selected, a menu with instructions is provided for all of the subroutines. Patient information is entered through the keyboard and when completed a prompt is given indicating information entry is finished and to run the engine. At this point the software engine(s) selected engages the central processing unit and begins operations.

Metastatic Interface Communication to Connector Module

The user interface activates the connection module program and uses input received from the user to make decisions and gather information from various databases to execute programs selected by the user in the numerical solution module. Reports and information from other modules in the invention, tumor origin, cellular module, colony module, tissue module, tumor module will be retrieved from their interfaces if needed automatically as part of the program. It is envisioned that information and report links will exist between the molecular, cellular, cellular expansion, pre-neoplastic , neoplastic interfaces and the numerical solution module subroutines in the metastatic module to facilitate exchange from other parts of the invention so calculations and descriptions can be performed.

Modification and Customization of Variables in the Metastatic Module Subroutines

All of the Metastatic Module's subroutines may be stopped and input parameters modified at points along the time line of operation according to the instructions at the user interface, and then allowed to continue provide human cancer simulation reports with a record of when and what modifications were made to input assumptions.

Default Parameters/Pre-Programmed Inputs in the Metastatic Module Subroutines

As with other modules described in the invention, the metastatic module subroutines and the algorithms within them will have pre-programmed default parameters in the event that information supplied by the user is

incomplete. This default parameter will allow the subroutines to run and/or instruct the user saying that the program subroutine cannot operate.

Connection Module Communication to Numerical Solution Module of the Metastatic Module

The connection module retrieves information from the databases, other module output reports as necessary and synthesizes it with the patient input from the user so subroutines within the numerical solution module can begin generating information relating to the future course of human cancer within the human body.

Connection Module/Database Operation in the Metastatic Module Subroutines

The connection module will be engaged whenever the input from the user is completed and the subroutines are designated to start. The connection module will process the input from the user and gather information from the various databases necessary for the execution of the mathematical and descriptive algorithms within the various numerical solution modules and transmit it to its proper location. If the program is stopped at the user interface along any aspect of the time line, and input is modified, the connection module will again automatically be engaged and then the new information will be gathered and transmitted to the numerical solution module for sequential processing. If the program is paused, the connector module will not be engaged.

Numerical Solution Module(s) in the Metastatic Module Subroutines

The numerical solutions module(s) carries out the generation of results and information for the reports. Once started they will complete their calculations, generate results and their reports and return them to the user interface for viewing on the monitor or for printing as per the computer hardware description. If continual output is chosen and the user stops the program the numerical solutions module (s) will store results generated up to that point in time or report if requested. If the program is restarted it will begin where it left off, include the changed parameters in the next sequential report, continue calculations with modified parameters and produce the report. If paused the numerical module will resume its calculations when the pause is ended and generate its results and report.

Results and Reports/User Interface in the Metastatic Module Output Subroutines

The final result of Metastatic Module and its subroutines will be a series of informational reports from the numerical solution modules and the information gathered from the databases to assist in running the mathematical and descriptive algorithms, continuously reported or sequentially reported, summarizing results or providing information at continuous or pre-selected discrete time intervals by request of the user along the time line of the human cancer virtual simulation engine's operation domain through the user interface. Similarly the reports can be requested by the user at various points in the future, along the time line of the operation of the module so that information generated by these subroutines can be reported. If the Metastatic Modules subroutines

are stopped and restarted the report will contain the sequence of information generated by the numerical solution modules in the order of the instructions received and containing the modifications for ease of understanding by the user.

Specific Operation Example of the Metastatic Module and its Subroutines

As an example of use, imagine a physician who wishes to examine the possible metastatic behavior of a patient's breast cancer through the human cancer virtual simulation information engine. Information will be generated by the engine to help answer two questions, is there an optimal time to administer the adjuvant therapy? What kind of reoccurrence scenarios on the microscopic (micro metastatic) and macroscopic (distant metastases) level may occur in the future?

1. After the program is started the user would be prompted by the start-up screen from a menu at the user interface to select the module to be used. The Metastatic Module is selected.

2. Next the three selections of metastatic module subroutines would appear, statistical and clinical outcome extrapolation, molecular biological and cancer origin/run forward. For this example the user would select all three.

3. Next the user interface would ask how many models were desired to be run by the engine in each subroutine. The physician is interested in looking at the potential outcomes for a prediction of an excellent to a moderate response to a single course of treatment so she selects two models for each.

4. Next the user interface would ask which model is to be run first and if continuous reporting was desired. If continual reporting was desired, the interface would ask which subroutine was to be run first. The user interface will allow one subroutine to operate continuously on display with a selection of desired parameters of information continually reporting the selected information. The user could select all the information that the subroutine is capable of producing or be limited to the selections the user makes. The subroutine would allow for this. For simplicity we will say that the user wishes to run the clinical and statistical outcome, molecular biological and cancer origin/run forward in that order and two models for each to allow for variation in the treatment regimens and assumptions for the models. We will assume that the user in this example requests that final reports be produced, not continually displayed, although at the end of this example we will demonstrate the continual display option as a replay of one of the stored programs.

5. At this point, the user interface will display a menu of inputs needed for the statistical and clinical outcome extrapolation. The user will be requesting information about the patient's name, height, weight, age, treatment steps such as chemotherapy, surgery and radiation; when treatments are planned, when treatment's took place, patient response to treatment or estimates thereof, initial tumor size and volume, tumor geometric shape, tumor location, health conditions of relevance to patient such as HIV status, immune system strength through secondary biomarkers such as white blood cell and T-cell count, family history of relevance to cancer epidemiology, other complicating factors or diseases, local and distant metastases location, biomarkers of human cancer such as estrogen receptivity in breast cancer and others, mitosis rate, cell diploidy, etc. Additionally it is envisioned that some of the input information may change and improve as the engine is developed, or may be tailored for certain kinds of cancer to provide better predictive and prognostic information to the user. For

instance, for the breast cancer patient example, in addition to the information above a prompt may appear to request staging of patient 1-4, specific questions related to the staging such as numbers of lymph nodes involved if radical or modified radical mastectomy has occurred, the presence of the BRCA1 gene, p53 tumor suppressor. gene activity in the tumor, HER 2 new expression, breast micro calcifications from X-ray, date of first estrus, menstruation cycle and other factors that could be useful for subroutine algorithms. The user enters this information and if unavailable a prompt for default will be provided with any additional instructions. The user is then prompted to go to the next step, the selection and customization of the report.

For this example we will say that the patient is a pre-menopausal 40 year old African American woman with a discovered 2.5 cm pear shaped invasive ductal carcinoma tumor with micro calcifications in her right breast. The tumor is removed and biopsied. The tumor was showed mild vascularity and the margins around the biopsy sample were not clean indicating spread beyond the tumor. The pathology report indicated HER 2 new expression, p53 loss, estrogen receptivity, a mitosis rate of 1 due to a low S phase fraction, tumor cell DNA intact (high diploidy) and good cellular differentiation, by some factors a slow to moderate growing tumor but invasive. Due to micro calcifications and of the other tumor factors that indicate the tumor may be active, breast conservation surgery is abandoned and the breast is removed and lymph nodes sampled, no lymph node activity is seen and the patient is classified as a stage 2 patient. The physician has entered all the above information into prompted questions from the program. She is considering adjuvant chemotherapy and the type and time to administer it. The adjuvant therapy she is considering will be the standard Cytoxan, Methotrexate and 5-Fluorouracil (CMF). The woman is healthy in all other respects. The physician will enter two scenarios into the metastatic program, one in which the patient response to chemotherapy will be considered superior, the other where it is moderate, a reflection of the aggressive genetic tumor factors versus its similarity to normal cells by good cell differentiation and only a low mitosis grade, making it more difficult to eradicate with chemotherapy. As stated earlier, information will be generated by the engine to help answer two questions, is there an optimal time to administer the adjuvant therapy? What kind of reoccurrence scenarios on the microscopic (micro metastatic) and macroscopic (distant metastases) level may occur in the future? The Metastatic Module will assist answering these two questions.

6. The physician now sees a menu of other report selections from the metastatic clinical and statistical outcome subroutine on the screen before her. The possible reports available to her include a) metastatic occurrence, target organ and percentage possibility, b) percentage disease free survival, c) micro metastatic and metastases volume, d) projected cancer cellular mitosis phase table, e) projected blood biomarker concentration over time. By keyboard selection the physician chooses all five.

7. After the physician enters the basic patient information and selects the reports to be issued, she will see a menu screen with a variety of options to provide the information back in the form of reports. The first selection is the final time domain of the engine's simulation. This is the point in the future from the present that the subroutine programs selected should end their calculations and generate results. This could range from short periods of time of days to approximately 20 years. The upper limit may change and will be bounded by the scientific information available to provide information useful to the subroutine calculation. The lower range will be determined by the information the engine could produce that would be of value beyond observation. Each

simulation would be bounded by time but for example, the user could chose five metastatic simulation each with longer and longer time frames, or stop the simulation at various points and request a report or begin new simulations with a desired new time frame sequentially on the previous one. For this example we will say the physician user requests a 5 year projection for the two simulations and display the information for the first six months by day for subroutine d) the projected cellular mitosis phase table. This enables information to be provided about follow up in reasonable time increments to be estimated from the engine's programs, given the young woman's age, medical aspects of the case and the fact that follow-up adjuvant chemotherapy is being considered.

8. Now the interface prompts the physician to begin and she hits start. The invention does the rest of the work until the reports appear at the user interface. That sequence of events is described next.

9. The computer now engages the connection module, a computer software program which takes the information supplied by the physician about the patient and extracts information from the epidemiological database and other databases as needed and automatically transfers retrieved information to the five numerical sub-module selected.

10. The numerical sub-modules automatically conduct their calculations and descriptions using their algorithms and other aspects of their programs, produce their reports and send them to the user interface.

11. After the engine has completed its work as described in steps 9 and 10, after starting the program in step 8, what the physician would receive, in this example first, is five reports for two simulations from the clinical and statistical outcome subroutines. Each is described here in example of what the inventions subroutines could produce with a visualization of what could appear in the content and its possible decision making value: Metastatic occurrence, target organ and percentage possibility. This report would contain a table of the target organs of reoccurrence, as an estimate this would be the left breast, chest wall, lungs, skeletal system and brain among others, with a percentage range in the 5 year time frame selected that reoccurrence would appear in various organs for the two scenarios selected. The optimal response would likely contain a lower percentage but given other factors in this case and the evaluation of information from the epidemiological database the percentage differences may be great or small and provide useful information for follow up. The report would be structured in a table of predictions at 6-month intervals in this example.

Percentage disease free survival. The report would provide an estimate of no reoccurrence for the optimal and moderate breast cancer patient response scenarios. It is envisioned that confidence intervals could be applied to this value based on the information in the database to allow better statistical value. Mortality and morbidity statistics would be reported in 6-month intervals over the 5-year time frame, in this example the optimal and moderate response scenarios could be compared and contrasted. Again the examination of the database information may show large or small differences, and possible improvement in the lessening of reoccurrence in certain organs over time. This could be reported positively to the patient and helps with decision making about follow-up activity.

Micro metastatic and metastases volume. This report would estimate the size, shape and potential volume of a recurrent tumor in the various target organs in six month increments over five years in a tabular format. The report would also indicate an estimate of the total micro metastatic volume, or an estimate of the total cancer

localized in tumors and non-localized within the whole body and in organs at given times in a tabular format. The value of this report would be an indication of when cancer mass may be large enough to be detected by various imaging techniques or other means in distant organs. In this example the physician would have an indication, say in the left breast, when micro metastasis would reach a point where micro calcifications may appear in the breast before small tumors in a mammogram appear in a moderately responsive patient. This could assist the physician in optimal timing patient follow-up for maximum probability of detection of any cancer spreading. If follow up mammograms are performed and micro calcification are not seen at the times predicted, this could be used as an indication of more optimal response to therapy, assisting the physician by focusing parameters for the subroutine assumptions in this invention if future simulations are conducted in the future.

I. Projected cancer cellular mitosis phase table. This report would contain an estimate of populations of cancer cellular growth, cancer cell death, and micro metastatic growth in terms of numbers of cells in various phases of cell division in the whole body and various target organs. What the physician would see, in this example since a daily report over the next 6 month time frame was selected would be a daily table indicating the number of potential cancer cells and what phase of growth or division they were in for the two optimal and moderate response to chemotherapy.

In this example chemotherapy has not been administered yet, but the physician is estimating potential responses. Also we know that the cell grade, mitosis rate and general DNA structure are fairly intact. Therefore, for example, we would expect to see a table representing shallowly rising curves indicative of a slow doubling rate. Given the more regular, rather than erratic cell reproduction rate, an estimation may appear in the daily tables indicative of high points when the remaining micro metastatic cancer left after surgery would be in certain phases of reproduction or cell cycles. The physician could use this information in the near term to plan to administer chemotherapeutic drugs so that the maximum concentration of the standard CMF regimen would be available in the target organs or whole body to interfere or destroy the cancer the best. In short this information may help physicians estimate how to get the medicine where and when it is needed most. She may even plan smaller dosages of chemotherapeutic agents in the regimen at later times and specifically to target organs to correspond to estimated cancer cellular peaks to destroy potential remaining cells, not caught on the first go around with a particular agent or to improve the effectiveness of response in a sub-optimally responding patient. This could be especially useful in the case of breast cancer patients in the use of Adriamycin, which has cardiotoxic side effects at high dosages but is one of the most effective anti-cancer agents. Adriamycin and possibly other chemotherapy agents could be timed and effectively used at large, as well as smaller dosages, for maximum positive effect while diminishing negative side effects.

Projected blood biomarker concentration over time. The report would estimate the concentration in nanograms per milliliter of a variety of cancer biomarkers in the bloodstream at six-month interval over the 5-year time period selected in this example. This area is new and ripe for discovery and will be a more valuable piece of report information in the future than today. For this example possibly the presence of HCG (human chorionic gonadotrophin) would be listed since it has been implicated with many cancers, CEA (carcinoembryionic antigen) has been shown to rise in severely metastatic breast cancer patients but current test methods may not be sensitive or the CEA may not expressed sufficiently to be useful for a stage 2 breast cancer

patient at this time. Others may provide useful indications of microscopic molecular activity indicative of micro metastasis. What the physician would see in the reports would be two estimates based on an optimal and moderate response of concentrations of chemicals that could be present in the bloodstream pertinent to the cancer selected and a report of other metabolic factors deemed useful for predictive and prognostic applications.

At the conclusion of reading the reports, the physician decides she would like to view the projected cancer cellular mitosis phase table in a continual fashion. She would only need to request that of the user interface when the program is brought back to start in step 4.

The process for the physician in this example steps 1 through 11 and the process of the operation of the invention in carrying out its functions is the same for the other two subroutine modules, the molecular biological and the cancer origin/run forward with the same title reports issued back to the user interface.
Because the underlying assumptions and the mathematical and descriptive calculation are different in these numerical modules, as described earlier in the numerical module section for the metastatic module in total, the reports may reach similar or very different conclusions. For example, it is fully expected that because DNA and molecular mathematical and descriptive algorithms are used to generate the information in the molecular biology and the cancer run forward metastatic subroutines that predictions in the cellular mitosis, micro metastatic volume and biomarker reports will be more precise and capable of generating meaningful predictions down to single cellular cycles and will vastly improve over time. Initially the statistical and clinical outcome extrapolation will provide the most useful predictions for disease free survival and distant metastases, target organ and probability predictions because it is based on real world information and subject to less uncertainty. All three approaches provide useful information for comparison against real world patient behavior, decision making and for research and educational purposes.

For ease of usage, the input to run all three metastatic sub-modules and their five numerical solution subroutines is envisioned to be the same. So the user need only enter the information one time, or can modify parameters and input selectively and generate 15 reports for human cancer metastatic behavior, or 5 reports each to provide predictive and prognostic information from 3 modeling approaches.

The Metastatic Module and all its subroutines and the mathematical and descriptive algorithms include a plurality of components to provide information that simulates the functions of living systems, in this case the behavior of cancer in the human body. The preparation of these modules is not a static occurrence and the numerical solution modules and the invention's databases, will be subject to modification and improvement with advancing scientific knowledge. Information supplied by these modules can be used to drive animations or other types of visual display beyond tables and reports to provide informative visualization and expression of the predictive and prognostic information that is derived from them.

DATA FLOW TO MODULES

Fig. 11 is a block diagram illustrating the types of data and information sent to each of the modules from a user interface (GUI) and from a patient information database. For each patient, the user inputs into the tumor origin module data and results of genetic tests, family history information, and information pertaining to life style

(smoking, drug use, etc.). The tumor origin module also receives from the database information on genetic relationships and possible mutations, including data on protein reactions relating to the synthesis of genetic material, and genetic information related to the interaction between cells in a normal environment, such as cell adhesion, intracellular structure, etc. The tumor origin module further receives statistical data from the statistical database regarding which genetic markers should exist and which genes, if any, are mutated.

The cellular module receives from the databases data pertaining to cell life cycle control, such as which genes are responsible for cell cycle control, for example Cyclin Dependent Kinesis (CDK), statistical data on cell cycle control and physical properties of cells, and data pertaining to the compounds and associated concentrations required for proper cell function.

The colony module receives from the databases data related to the interaction between cells, such as the identification of genes responsible for cell interaction (e.g. for production of proteins used in cell adhesion, etc.), the identification of genes responsible for physical properties of cells (e.g. cell shape and size), and statistical data concerning cell interaction (e.g. cell bond strength, nutrition distribution, etc.), and genetic information responsible for cell structure (e.g. cell cycle, bond strength, membrane strength).

The tissue module receives from the databases data related to the proteins and other biochemical compounds and elements involved in the interaction between cells and in tissue structure, both in a normal environment and in a malignant environment, and other genetic and protein/biochemical information not specific to metastatic spread.

The tumor module receives from the databases data related to genetic, biochemical and statistical information concerning cell cycle, bond strength, membrane strength, tissue structure, interaction between cells, etc. in a malignant environment.

The metastatic module receives from the databases data relating to the mechanisms of metastatic spread, and statistical data relating to cellular activity, both specific to metastatic spread and generally.

DATA FLOW BETWEEN MODULES

Fig. 12 is a block diagram illustrating the types of data and information passed between the various modules and between the user interface and database. The subroutines of the tumor origin module develop from the inputted data, data relating to cell cycle rate, genetic changes in cellular DNA, and protein expression. This information is inputted to the cellular module for use in the cellular module subroutines. The tumor origin module also develops diagnosis data from the inputted patient information and relevant data from the databases, concerning possible genetic changes and expression of unusual proteins as indicating possible staging of disease.

The cellular module subroutines utilize the information developed by the tumor origin module to calculate cell cycle rates, genetic changes and protein expression on a cellular level, and to determine cell size, shape, growth rate, and protein expression related to cell structure. This information is passed to the colony module, where the subroutines of the colony module use this information in conjunction with the data received from the databases to calculate cell structure, size, shape, etc. of a tissue matrix, which information is inputted to the tissue module.

The tissue module in turn utilizes this data to calculate the size, shape, structure, bond strength, etc. of

tissue, which information is passed on to the tumor module. The tumor module in turn utilizes this information to predict tumor growth, shape and size, etc. into the future. The metastatic module takes the tumor-related information and utilizes it to predict metastatic spread of carcinogenic cells to other systems of the body into the future.

DATABASE FORMATION, UPDATING, AND MODEL DEVELOPMENT

Fig. 13 is a block diagram illustrating the building and updating of the various databases used in the HCVS system. As shown, data from various external sources, such as research and development institutions, medical and scientific journals, textbooks, university databases, public and private databases, public research institutions, research laboratories and insurance companies, is inputted to an error screening module for filtering of the data to eliminate erroneous, irrelevant or incomplete data. The filtered data is then inputted to data type distribution module which separates the data and groups it by type, such as input data, relationship data, or output data, and formats the data into a matrix. The data matrix is then inputted into a modeling data spreadsheet module for preparation of data sets. The data sets are then inputted to a learning system module, for development and updating of the various models used in the subroutines. The models are stored in a model staging storage memory, from which they are inputted to the application environment of the system, for use with the specific patient information to calculate diagnosis and predictive results which are then displayed to the user on a graphical user interface.

CELL CYCLE ALGORITHMS

Fig. 15 illustrates a general algorithm for determining particular protein expressions in cell life cycle process. At step 150, the maximum possible amount of protein capable of being produced by the cell under study. At step 151, the percentage of this maximum possible amount being produced is calculated. At step 152, it is determined whether any other processes are involved upon which protein expression is dependent. If not (step 153), then the determined protein concentration is outputted at step 154. If it is determined that protein production is dependent on a following process (step 155), at step 156 the calculation is paused to await the information from the following process, and at step 157 the needed information is imported from the following process algorithm, and the process advances to step 160.

If it is determined (step 158) that the following process itself is dependent on the protein at issue, then at step 164 the calculated protein concentration is outputted. If it is determined (step 159) that the protein at issue is dependent on a previous process, then at step 160 the dependence ratio or relationship is determined. The value of the dependence is then determined at step 161 and the operation needed to simulate the dependence is selected at step 162. At step 163 the percentage of protein production controlled by the dependence is calculated, and the determined protein concentration is then outputted at step 164.

Fig. 14 provides an example of a cell cycle algorithm for calculating cell life cycle from the G1 (start) cycle phase through to the M phase. In each phase, the production of various free proteins such as cyclin A, cyclin B, cyclin D, cyclin E, Cdk 1, Cdk 2, Cdk4, and RB are calculated, according to the algorithm of Fig. 15. The results of each calculation are then used to calculate the next protein/ protein complex in the cell cycle phase,

leading to the production of growth factors. If complex failure is detected at any point during the calculation run, a cell cycle halt is triggered. The calculated growth factors are then transported as expressed growth factors to the next phase of the cell cycle.

Specific Operation Example of the Tissue Level Module and the Metastatic Module

In this example we will assume that a physician has a patient with a large colon tumor, 7 cm in diameter and the patient is 75 year old male in frail health. Given the health of the patient possibly radiation treatment may be a better option than surgery. The physician would like to use the tissue level and then the metastatic level simulation engine to examine the effects of radiation on the tumor and decide if this is a viable option for treatment in lieu of surgery.

1.First the program would be loaded as in the previous example and the physician would choose the tissue module and would see the pre-neoplastic interface, additionally the tumor module and the neoplastic interface and the metastatic module and the metastatic interface would be activated by the physician in this example.

2. The physician would then see the menu of options that would allow patient information to be entered.

3. The physician, similar to the response information in the previous breast cancer example, would have the option to estimate the response that radiation would have on the tumor and the surrounding tissues. For this example we will assume two scenarios, a simulation where no radiation treatment is given and a simulation where a high dose of radiation is given within a week of the simulation. In the operational version of the invention it is envisioned that a wide variety of parameters would be available to the physician based upon the latest indices of cancer radiation treatment to easily enable entry of the strength, type and dose of radiation and times of treatment to assist estimation of the number of tissue and tumor cells destroyed in the process.

4. The physician would then need to follow instructions and enter the types of reports he would like to see and the frequency of information from the simulation. For the tissue module example we will look at daily reports rate of mitosis, survival rates of cells and a daily readout of the projected cell mitosis phase report from the metastatic module for the next sixty days or two months.

5. The order of the reports that the physician requests are the no radiation treatment first, and then the high dose radiation treatment reports.

6. Once the patient tumor information is entered into the tissue module interface, the physician would hit the start button.

7. The engine now goes through the same process of taking the input to the connection module and then retrieving information from the inventions database necessary to run the algorithms in the tissue and metastatic level numerical solution modules, when the tissue level and metastatic numerical solution modules have completed their work, they produce the reports and send them back to the user interface.

8. What the physician sees at the user interface is six reports waiting to be reviewed. Four related to the increase in tissue growth (rate of mitosis and survival rate of cells) from the tissue module in a no intervention versus a high intervention scenario. The last two would be an analysis of cell population, death and cell growth phases, with numbers of cells and times from the metastatic module's projected cell phase mitosis report for a no intervention versus high dose radiation intervention scenario.

The physician could, if desired, have activated other subroutines through the pre neo-plastic interface accessing the tissue module to generate reports such as physical properties of cells, nutritional consumption, cell bonding and intracellular structure. The physician could, if desired, have activated other subroutines through the neo-plastic interface for the tumor module to generate reports such as tumor mass, tumor growth rate, genetic mutations present and vascular construction. In this example the metastatic reports requested include some of these areas but not all.

The physician now has some comparisons of what the effectiveness of a high dose radiation treatment may be at the tissue level for a tumor of certain size and molecular biological properties characteristic of the individual patient. Several pieces of information can be gleaned from reports of this kind. For the sake of example we will explore them.

1. First in the no treatment example, the tissue level reports of projected cell mitosis phases and metastases volume can be very useful in estimating the behavior of the tumor in the next two months for treatment options. Is it slow growing or fast? Based on patient input what kind of mitosis pattern is expected in the next sixty days? Is the mitosis pattern in the tissue of the tumor periodic or erratic? The report we expect will have statistical information associated with the engines predictions based partly on the quality and quantity of the information inputted and also on the information available from the database to assist in its predictions and will help answer these questions at the tissue level. How does this compare with predictions in the metastatic module from its report?

2. The physician will have a readout of exactly one week from the present day on a kill off of the cancer cells in the tumor and then a projection of growth for the next 53 days after that. How much would the tissue metastases shrink?

3. Does the projected cell mitosis report indicate a pattern that would help in the optimal timing of a high dose radiation treatment? Radiation is most effective in disrupting and destroying mammalian cells when applied during the mitotic phase during actual cell division. The mitosis phase can be very brief and the shortest phase in the cell life cycle. Possibly the physician would see from the HCVS reports a period of statistically high mitotic activity within the tumor in 2 weeks or sixty day period and would delay treatment until that period. The invention could and most likely would be rerun to estimate the effects of radiation treatment on a colon cancer under these potentially better conditions to see what the effect would be.

4. Following the pattern of inquiry further, could lower doses at different times in the next sixty days be as effective as one high dose? Would there be a patient benefit? Again comparing the result of the two scenarios and the reports associated with each may indicate directly that this could be the case or point to the need for further simulations with the invention to fully explore radiation treatment effect on colon cancer tumor tissue in the near term.

In the beginning of this example we mentioned the metastatic module in conjunction with the tissue module.

As Fig 3 shows the linear progression of interfaces and modules, the next logical step to take would be to do a more distant metastatic projection on the patient. The physician would have two new pieces of information to achieve this, a scenario in the next sixty days that could be plugged into the metastatic module indicating no

treatment and projections could be made from the present line, second information on tumor shrinkage based on a high dose radiation treatment. The process would be the same as in the previous example for the metastatic module and once the metastatic module would be activated the interface would ask various question of value in making a longer-term prediction. At this point, the morbidity and mortality statistics from the clinical outcome report would be of interest

In considering this example, it is worth thinking that a logical process of usage of the information from this simulation would be for the physician to:

1. Examine the options and efficacy for radiation treatment using the tissue module simulation
2. Decide the best treatment at the tissue level and administer it
3. Compare the tissue level modules results against the actual patient response
4. Enter the patient actual response information into the metastatic module at a later time and validate or change assumption parameter for the metastatic module interface based on real world results to improve predictions and maximize the possibilities for a favorable outcome.

System Configuration

There are two general configurations for the HCVS system according to one preferred embodiment of the invention. The first of the two is medical. This is by far the most complex and interactive. The purpose and usefulness of the diagnostic, treatment, and research configuration is to deal with real life patients. This configuration will use the information entered into the HCVS to artificially generate in the computer a replication of the actual situation at hand. This configuration will run with preprogrammed cases of cancer. The purpose and usefulness of this configuration is to train and prepare present and future healthcare professionals. The second of the configurations is the educational configuration.

While particular specifics of the present invention have been disclosed, it is to be understood that various different modifications are possible and are contemplated within the true spirit and scope of the claims. All such modifications and variations of the invention herein described as would be apparent to those skilled in the art are intended to be encompassed within the following claims.

What is claimed is:

1. A computer-implemented system for simulating the occurrence and metastases of cancer in the human body, comprising:

a database containing information relating to genetics, molecular biology, statistics, and metastatics as applied to occurrences and metastases of human cancer;

an operator interface for inputting into said system information and instructions corresponding to patient data;

a plurality of program modules, each including at least one subroutine, for processing information and data inputted through said operator interface in conjunction with information obtained from said database, and outputting said information to said operator interface, wherein each of said program modules carries out descriptive and mathematical processes corresponding to different levels of human cancer biological processes, and information generated by modules performing lower level processes also is outputted to modules performing higher level processes, whereby predictive future cancer metastases as well as past origin of cancers are provided; and

an output device for communicating results of subroutine processing to a user.

2. The system of claim 1, wherein said system includes a medical applications configuration which allows diagnostic, treatment and research human cancer simulations to be performed by accepting user inputted information, and an educational configuration using pre-programmed situations which allows interaction for medical student educational purposes.

3. The system of claim 1, wherein said plurality of program modules comprises six modules for simulating the biological process of a cell's transformation from a normal cell to a cancerous cell and then metastatic activity, the modules comprising tumor origin, cellular, colony, tissue, tumor and metastatic modules.

4. The system of claim 3, further comprising within each module subroutines that have responsibility over smaller descriptive and mathematical processes needed to simulate human cancer biology, each of the subroutines producing results in forms needed by the user to describe the biological process over which the subroutine has responsibility, said subroutines including:

a genetic mutation subroutine and diagnostic subroutine of the tumor origin module,

a cell cycle subroutine and a physical properties subroutine of the cellular module,

an interaction between cells subroutine and a structure subroutine of the colony module,

an interaction between cells subroutine and a tissue structure subroutine of the tissue module,

an interaction between cells subroutine, a tissue structure subroutine, and a physical properties of the tumor subroutine of the tumor module, and

a statistical and clinical outcome subroutine, a molecular biological subroutine, and a cancer origin/run forward subroutine of the metastatic module.

5. A computer-implemented method of simulating the occurrence and metastases of cancer in the human body, comprising the steps of:

collecting and providing information relating to genetics, molecular biology, statistics, and metastatics as applied to occurrences and metastases of human cancer;

providing information and instructions corresponding to patient data;

processing information and data related to a patient in conjunction with said information relating to occurrences and metastases of human cancer and outputting said processed information, wherein said processing comprises the steps of carrying out descriptive and mathematical processes corresponding to different levels of human cancer biological processes, with information generated by performing lower level processes being outputted to higher level processes, whereby predictive future cancer metastases as well as past origin of cancers are provided; and

communicating the results of processing to a user.

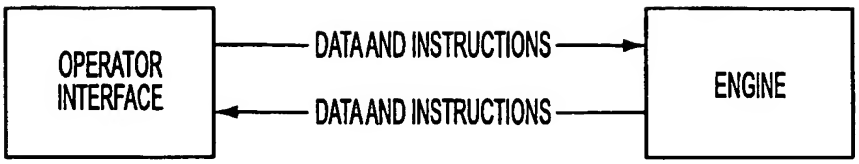
OPERATOR INTERFACE
DATA AND INSTRUCTIONS
DATA AND INSTRUCTIONS
ENGINE

FIG. 1

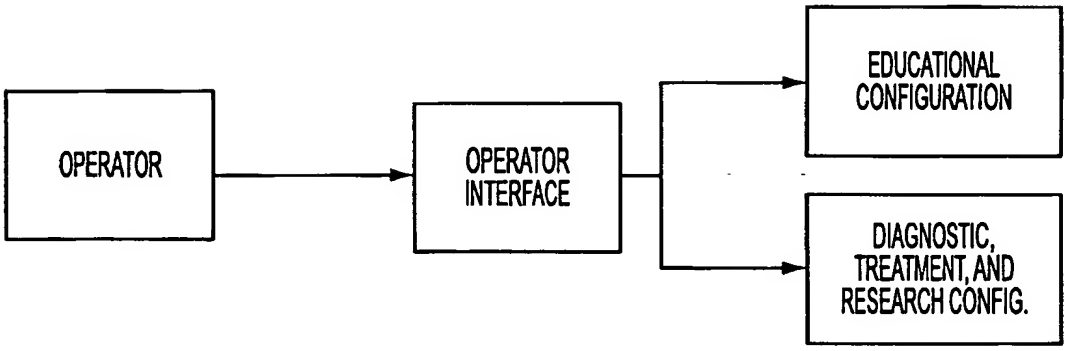
OPERATOR
OPERATOR INTERFACE
EDUCATIONAL CONFIGURATION
DIAGNOSTIC, TREATMENT, AND RESEARCH CONFIG.

FIG. 2

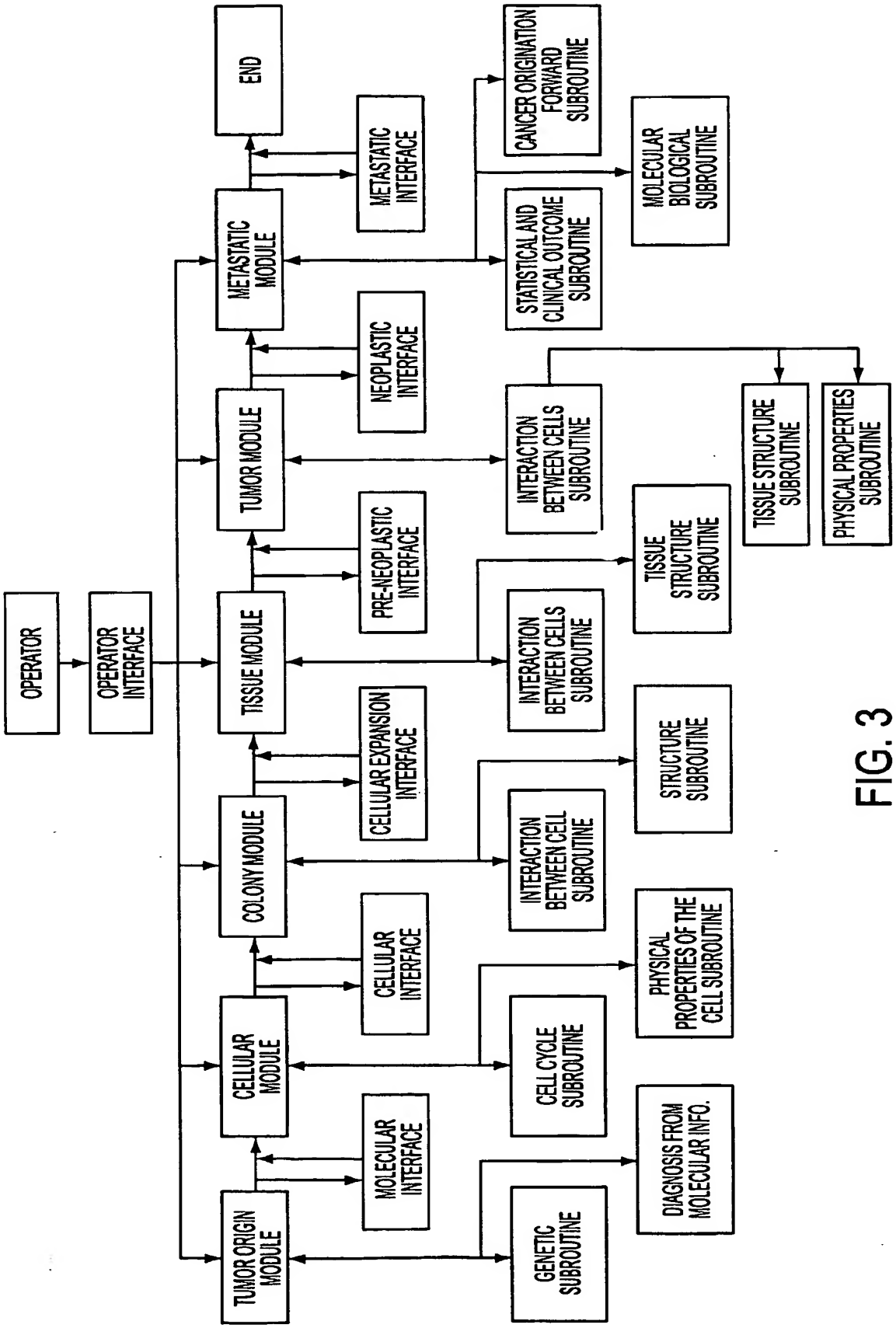
OPERATOR
OPERATOR INTERFACE
TISSUE MODULE
TUMOR MODULE
METASTATIC MODULE
END
COLONY MODULE
CELLULAR MODULE
TUMOR ORIGIN MODULE
PRE-NEOPLASTIC INTERFACE
NEOPLASTIC INTERFACE
METASTATIC INTERFACE
CELLULAR EXPANSION INTERFACE
CELLULAR INTERFACE
MOLECULAR INTERFACE
INTERACTION BETWEEN CELLS SUBROUTINE
INTERACTION BETWEEN CELLS SUBROUTINE
INTERACTION BETWEEN CELL SUBROUTINE
CELL CYCLE SUBROUTINE
GENETIC SUBROUTINE
TISSUE STRUCTURE SUBROUTINE
STRUCTURE SUBROUTINE
PHYSICAL PROPERTIES OF THE CELL SUBROUTINE
DIAGNOSIS FROM MOLECULAR INFO.
STATISTICAL AND CLINICAL OUTCOME SUBROUTINE
CANCER ORIGINATION FORWARD SUBROUTINE
MOLECULAR BIOLOGICAL SUBROUTINE
TISSUE STRUCTURE SUBROUTINE
PHYSICAL PROPERTIES SUBROUTINE

FIG. 3

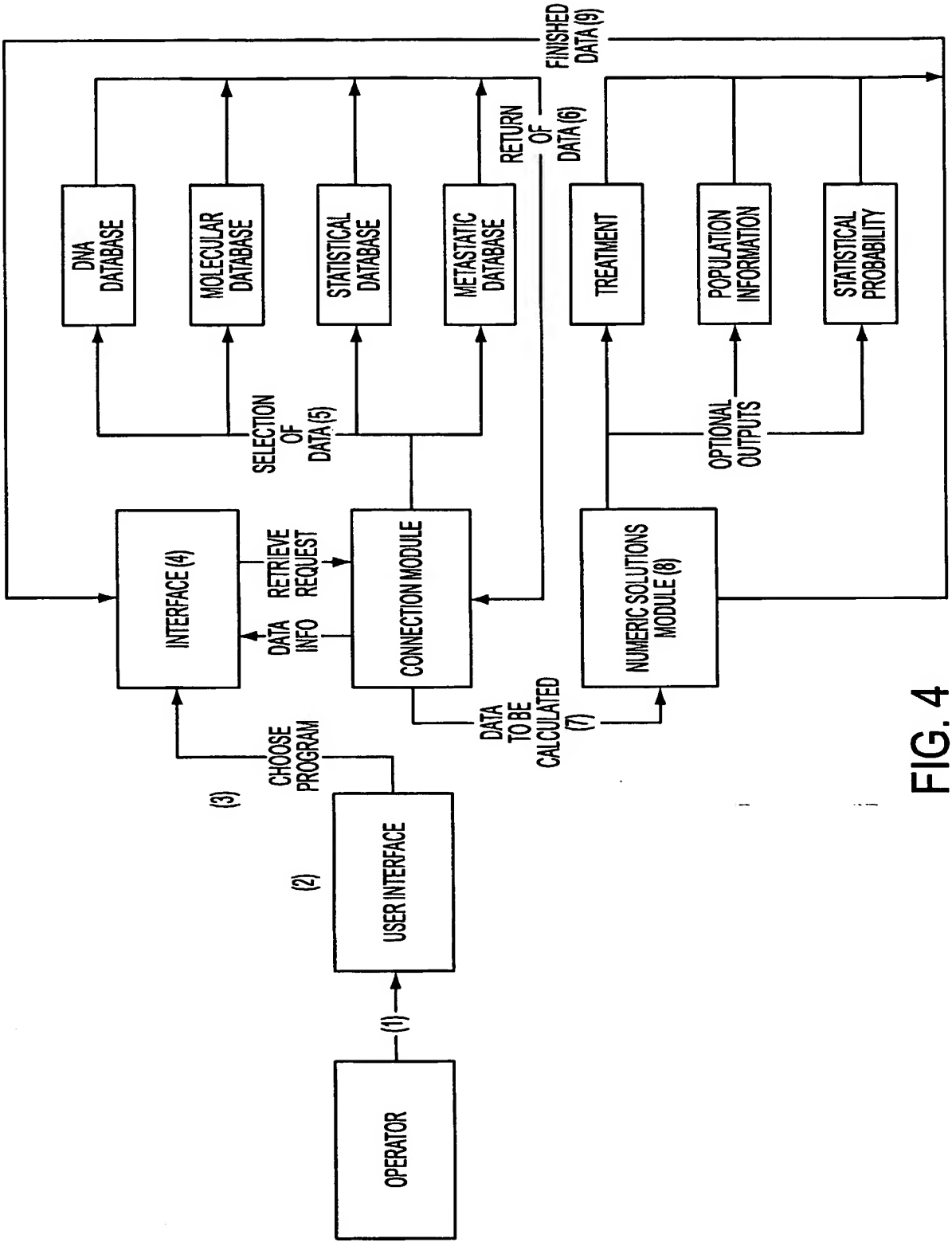
OPERATOR
(1)
USER INTERFACE
(2)
(3)
CHOOSE PROGRAM
INTERFACE (4)
RETRIEVE REQUEST
DATA INFO
CONNECTION MODULE
DATA TO BE CALCULATED (7)
NUMERIC SOLUTIONS MODULE (8)
SELECTION OF DATA (5)
OPTIONAL OUTPUTS
RETURN OF DATA (6)
FINISHED DATA (9)
DNA DATABASE
MOLECULAR DATABASE
STATISTICAL DATABASE
METASTATIC DATABASE
TREATMENT
POPULATION INFORMATION
STATISTICAL PROBABILITY

FIG. 4

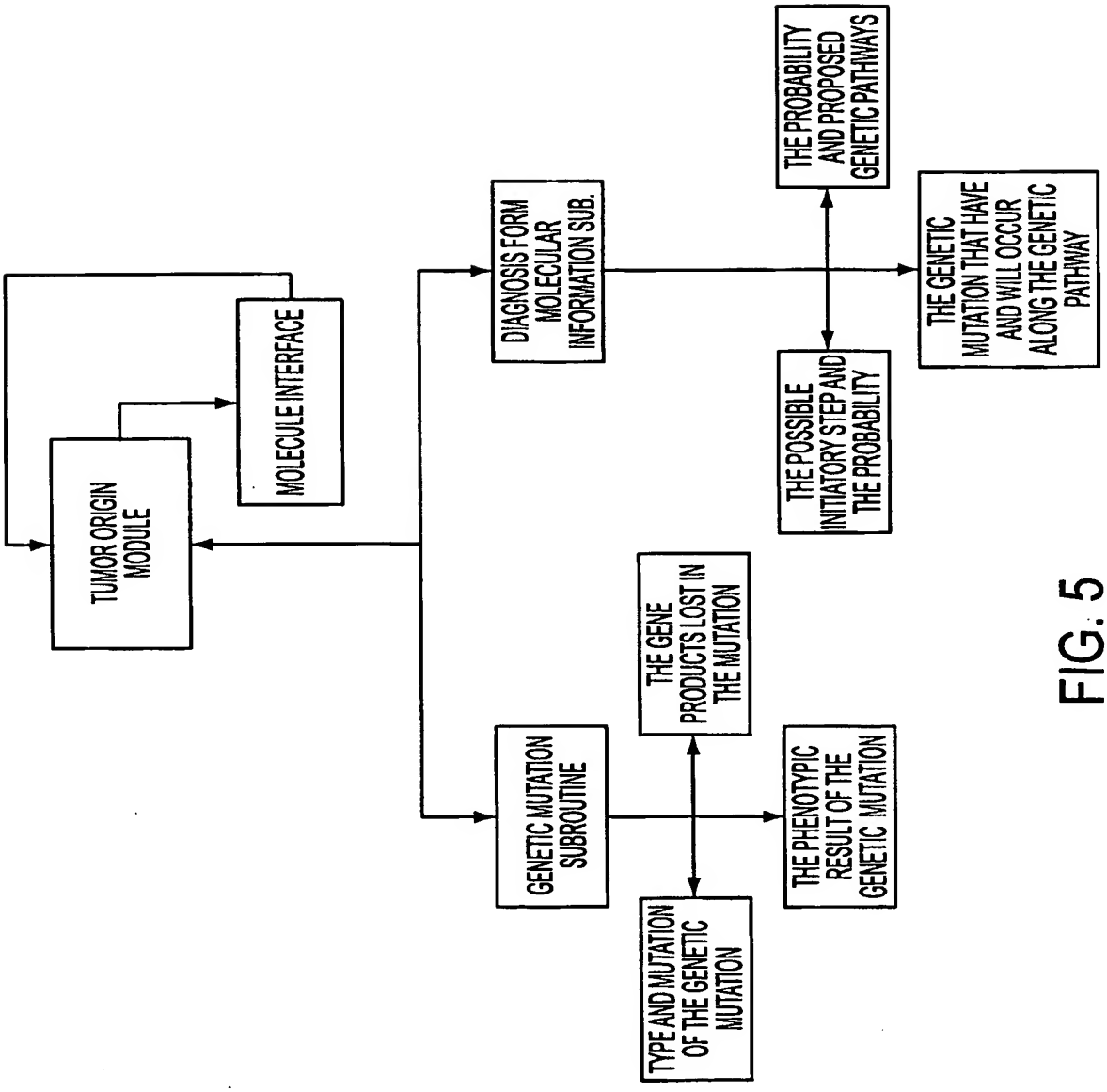
TUMOR ORIGIN MODULE
MOLECULE INTERFACE
DIAGNOSIS FORM MOLECULAR INFORMATION SUB.
THE PROBABILITY AND PROPOSED GENETIC PATHWAYS
THE GENETIC MUTATION THAT HAVE AND WILL OCCUR ALONG THE GENETIC PATHWAY
THE POSSIBLE INITIATORY STEP AND THE PROBABILITY
GENETIC MUTATION SUBROUTINE
THE GENE PRODUCTS LOST IN THE MUTATION
THE PHENOTYPIC RESULT OF THE GENETIC MUTATION
TYPE AND MUTATION OF THE GENETIC MUTATION

FIG. 5

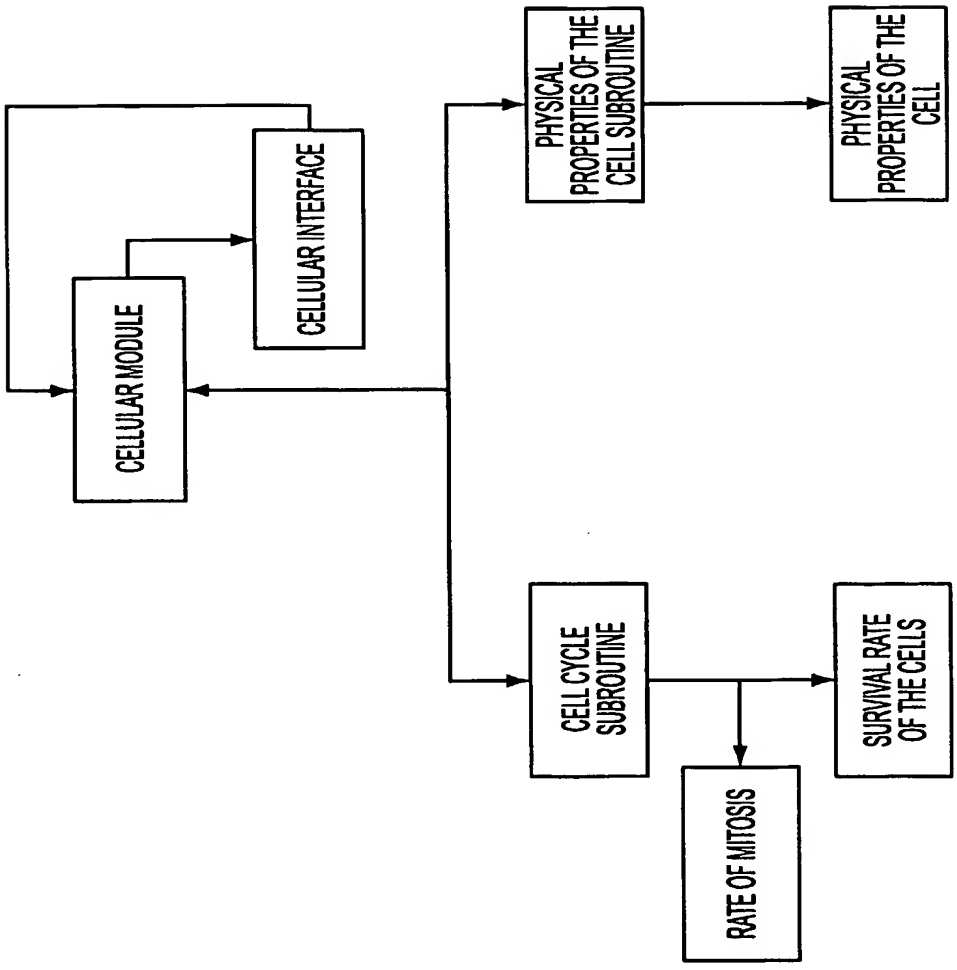
CELLULAR MODULE
CELLULAR INTERFACE
PHYSICAL PROPERTIES OF THE CELL SUBROUTINE
PHYSICAL PROPERTIES OF THE CELL
CELL CYCLE SUBROUTINE
SURVIVAL RATE OF THE CELLS
RATE OF MITOSIS

FIG. 6

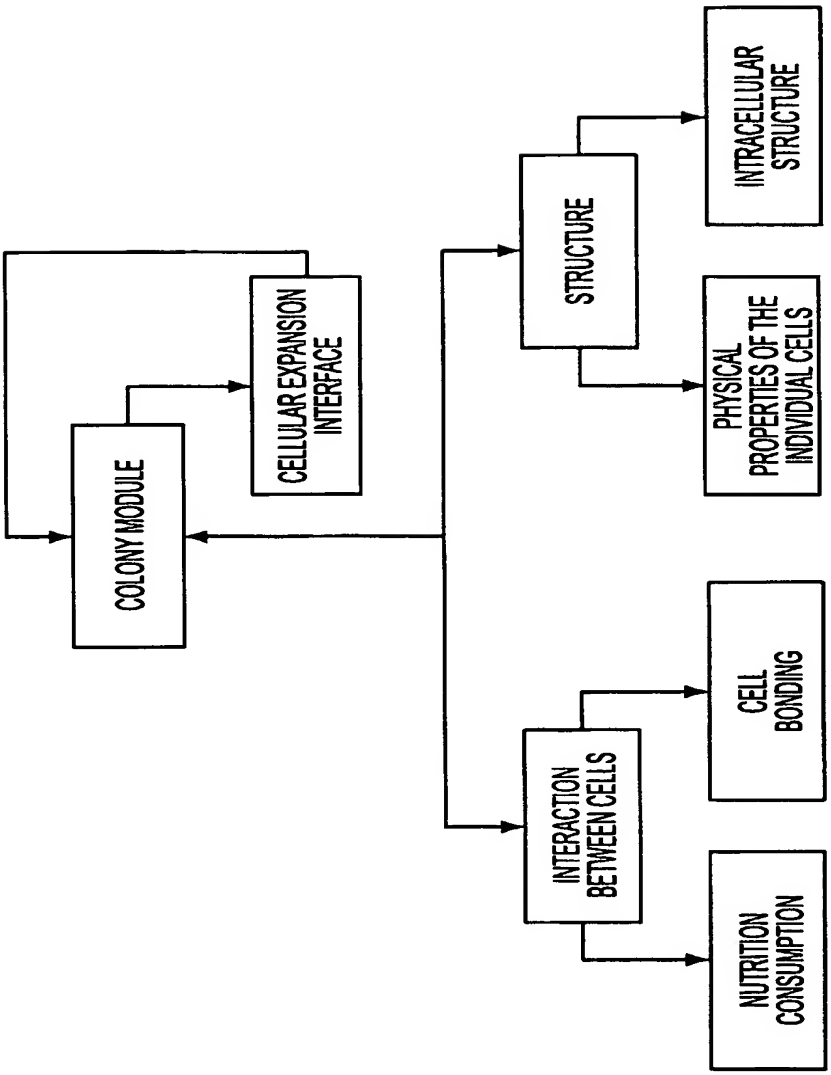
COLONY MODULE
CELLULAR EXPANSION INTERFACE
STRUCTURE
INTRACELLULAR STRUCTURE
PHYSICAL PROPERTIES OF THE INDIVIDUAL CELLS
INTERACTION BETWEEN CELLS
CELL BONDING
NUTRITION CONSUMPTION

FIG. 7

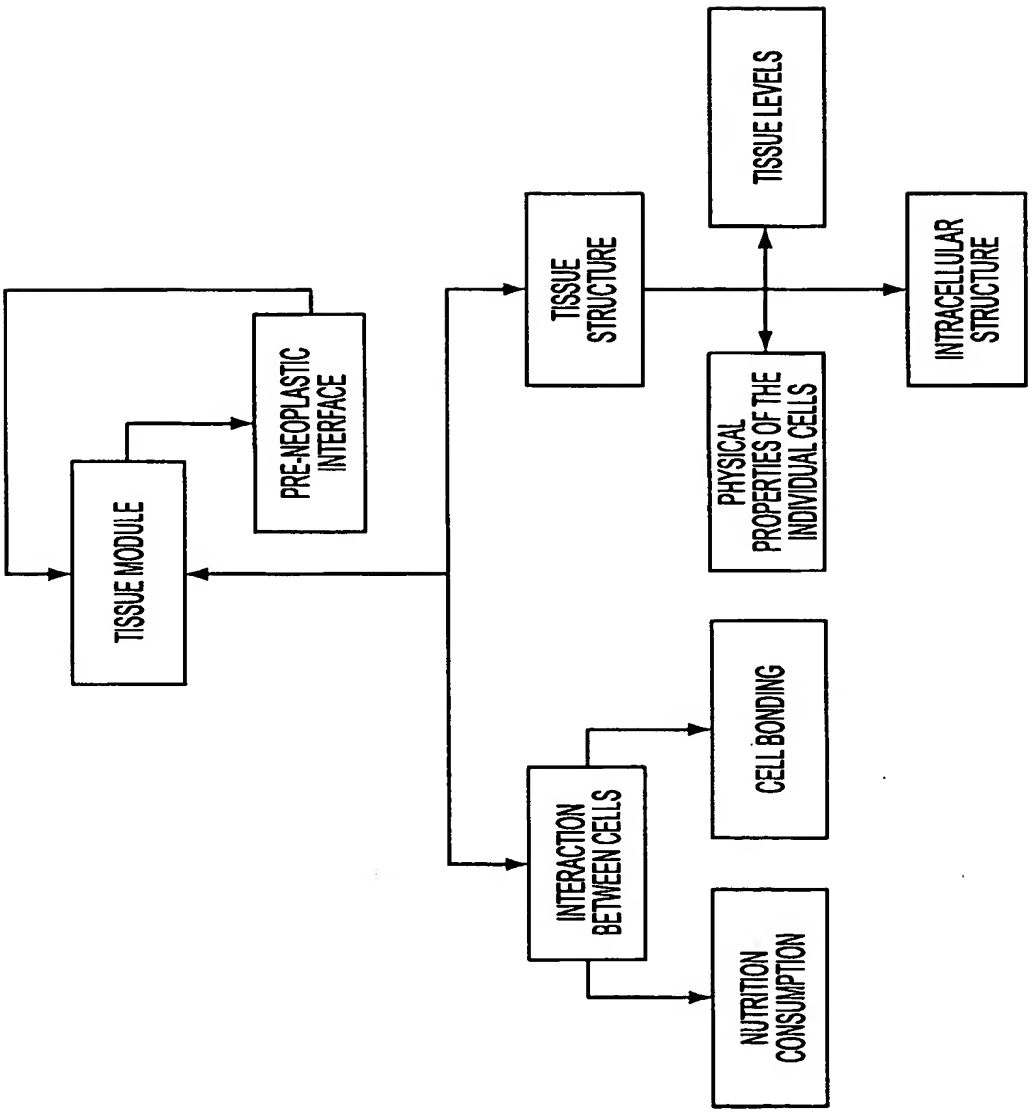
TISSUE MODULE
PRE-NEOPLASTIC INTERFACE
TISSUE STRUCTURE
TISSUE LEVELS
INTRACELLULAR STRUCTURE
PHYSICAL PROPERTIES OF THE INDIVIDUAL CELLS
INTERACTION BETWEEN CELLS
CELL BONDING
NUTRITION CONSUMPTION

FIG. 8

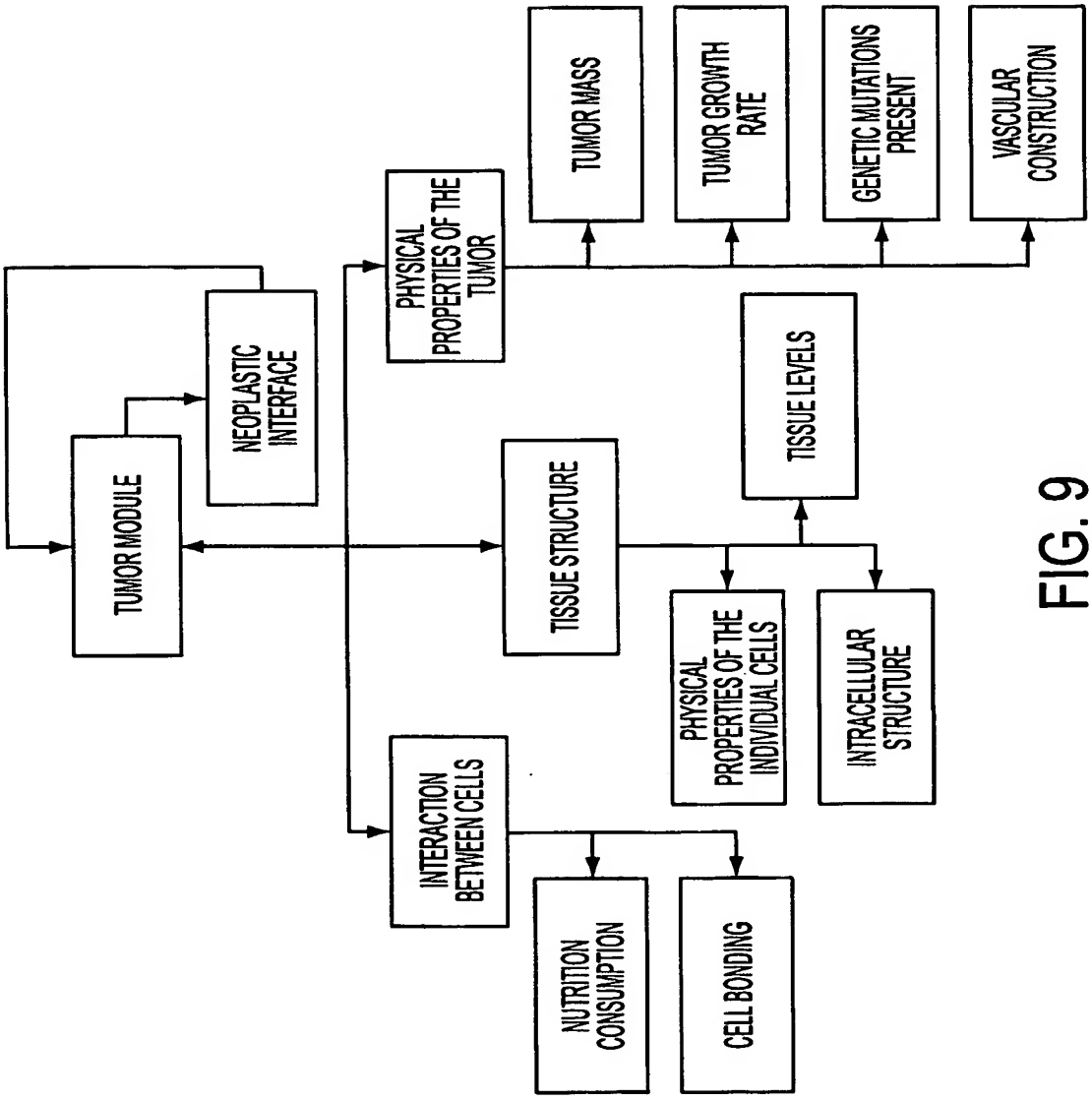
TUMOR MODULE
NEOPLASTIC INTERFACE
PHYSICAL PROPERTIES OF THE TUMOR
TUMOR MASS
TUMOR GROWTH RATE
GENETIC MUTATIONS PRESENT
VASCULAR CONSTRUCTION
TISSUE STRUCTURE
TISSUE LEVELS
PHYSICAL PROPERTIES OF THE INDIVIDUAL CELLS
INTRACELLULAR STRUCTURE
INTERACTION BETWEEN CELLS
NUTRITION CONSUMPTION
CELL BONDING

FIG. 9

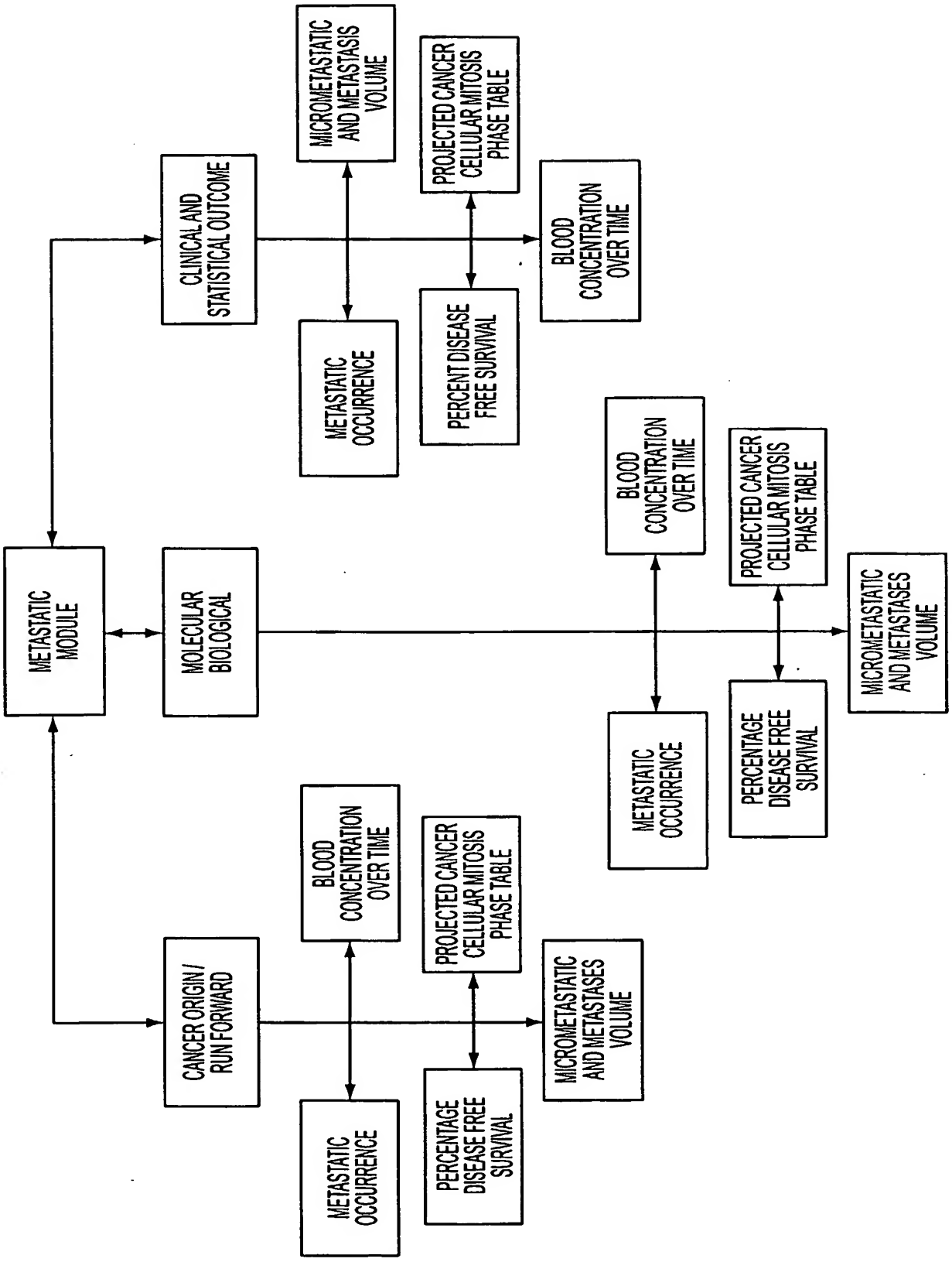
METASTATIC MODULE
CLINICAL AND STATISTICAL OUTCOME
MICROMETASTATIC AND METASTASIS VOLUME
PROJECTED CANCER CELLULAR MITOSIS PHASE TABLE
BLOOD CONCENTRATION OVER TIME
METASTATIC OCCURRENCE
PERCENT DISEASE FREE SURVIVAL
MOLECULAR BIOLOGICAL
BLOOD CONCENTRATION OVER TIME
PROJECTED CANCER CELLULAR MITOSIS PHASE TABLE
MICROMETASTATIC AND METASTASES VOLUME
METASTATIC OCCURRENCE
PERCENTAGE DISEASE FREE SURVIVAL
CANCER ORIGIN / RUN FORWARD
BLOOD CONCENTRATION OVER TIME
PROJECTED CANCER CELLULAR MITOSIS PHASE TABLE
MICROMETASTATIC AND METASTASES VOLUME
METASTATIC OCCURRENCE
PERCENTAGE DISEASE FREE SURVIVAL

FIG. 10

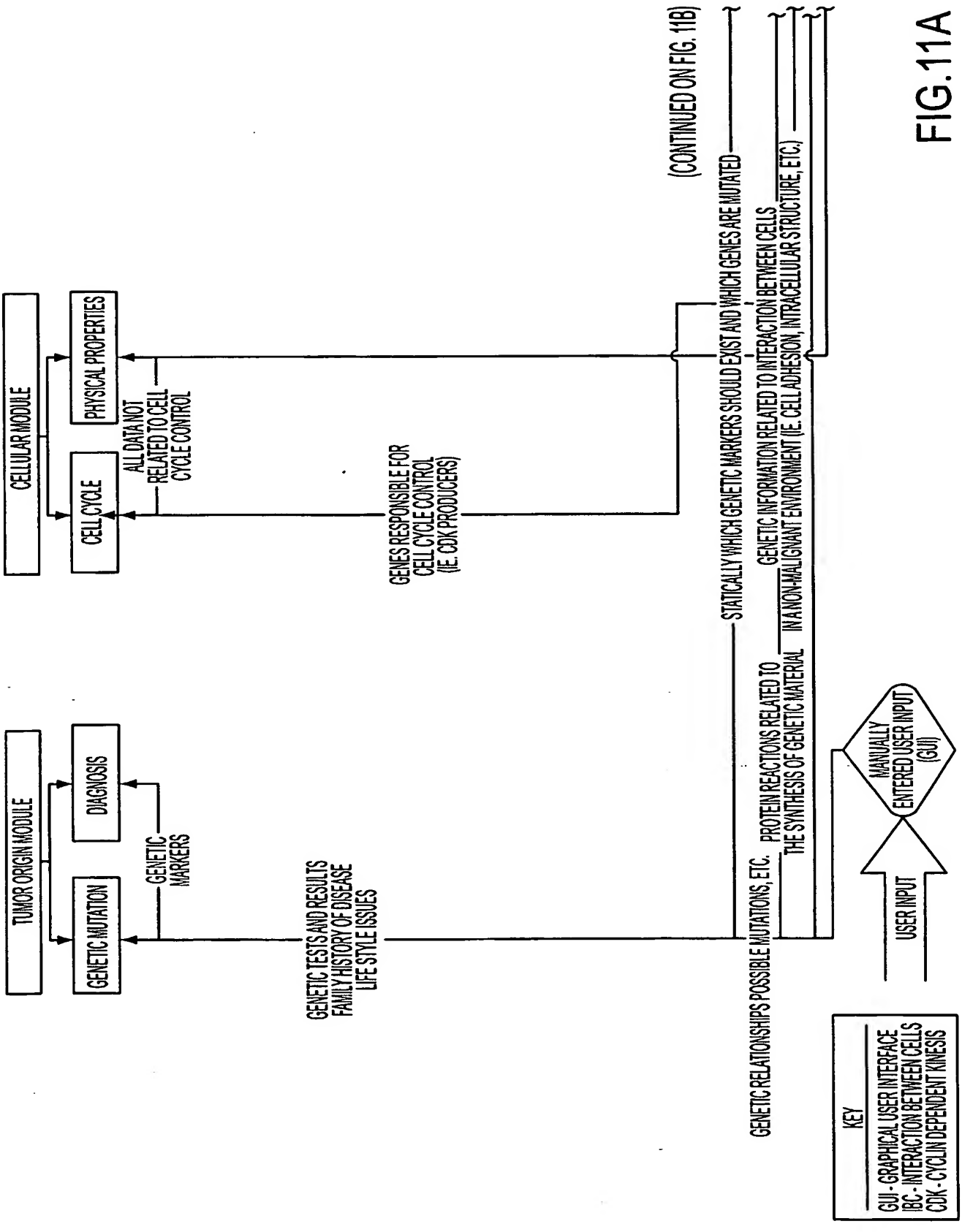
CELLULAR MODULE
PHYSICAL PROPERTIES
CELL CYCLE
ALL DATA NOT RELATED TO CELL CYCLE CONTROL
GENES RESPONSIBLE FOR CELL CYCLE CONTROL (IE. CDK PRODUCERS)
(CONTINUED ON FIG. 11B)
STATICALLY WHICH GENETIC MARKERS SHOULD EXIST AND WHICH GENES ARE MUTATED
GENETIC INFORMATION RELATED TO INTERACTION BETWEEN CELLS IN A NON-MALIGNANT ENVIRONMENT (IE. CELL ADHESION, INTRACELLULAR STRUCTURE, ETC.)
PROTEIN REACTIONS RELATED TO THE SYNTHESIS OF GENETIC MATERIAL
GENETIC RELATIONSHIPS POSSIBLE MUTATIONS, ETC.
TUMOR ORIGIN MODULE
DIAGNOSIS
GENETIC MUTATION
GENETIC MARKERS
GENETIC TESTS AND RESULTS FAMILY HISTORY OF DISEASE LIFE STYLE ISSUES
MANUALLY ENTERED USER INPUT (GUI)
USER INPUT
KEY
GUI - GRAPHICAL USER INTERFACE
IBC - INTERACTION BETWEEN CELLS
CDK - CYCLIN DEPENDENT KINESIS

FIG.11A

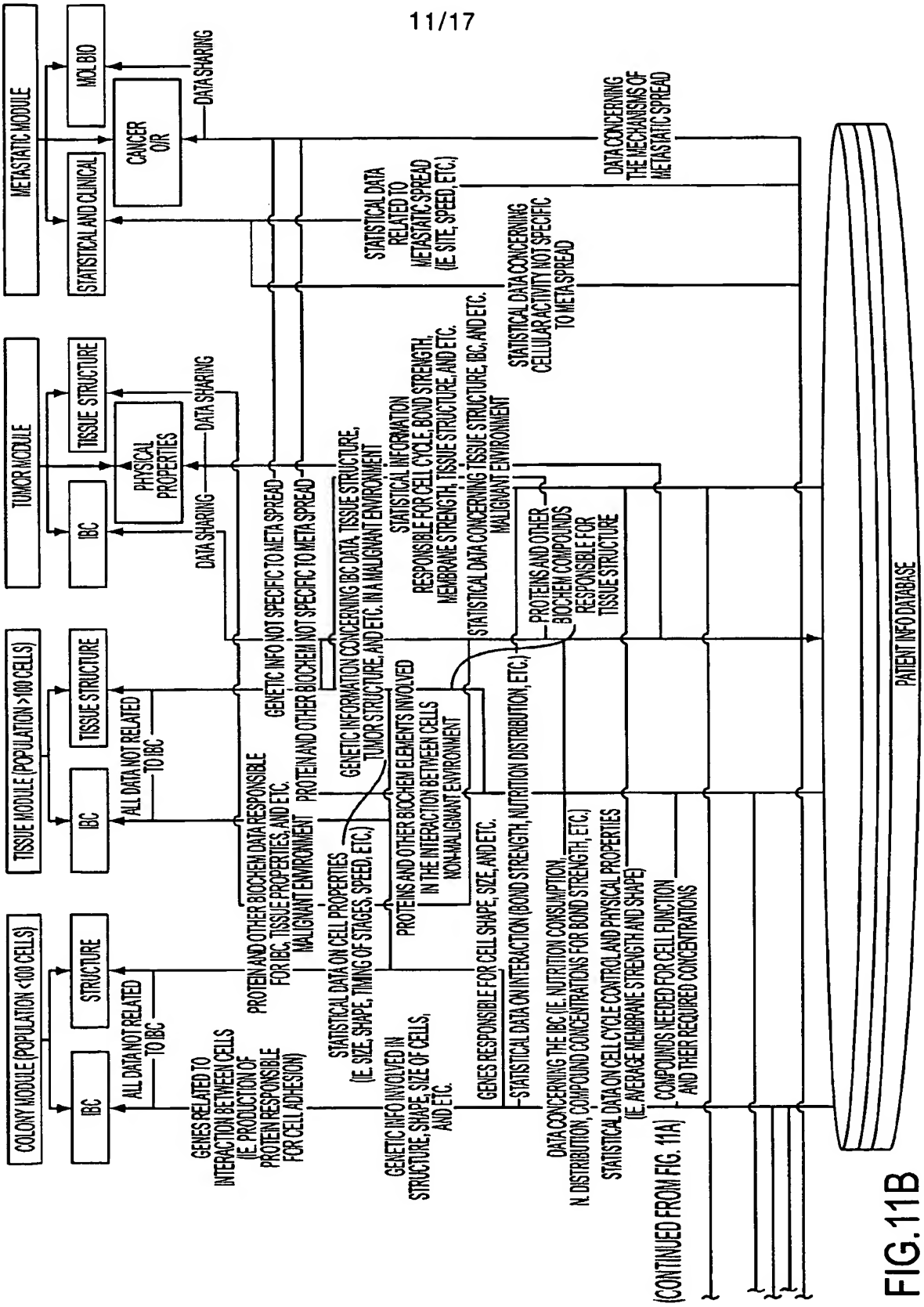
METASTATIC MODULE
MOL BIO
STATISTICAL AND CLINICAL
CANCER O/R
DATA SHARING
TUMOR MODULE
TISSUE STRUCTURE
IBC
PHYSICAL PROPERTIES
DATA SHARING
DATA SHARING
TISSUE MODULE (POPULATION >100 CELLS)
TISSUE STRUCTURE
IBC
ALL DATA NOT RELATED TO IBC
COLONY MODULE (POPULATION <100 CELLS)
STRUCTURE
IBC
ALL DATA NOT RELATED TO IBC
GENES RELATED TO INTERACTION BETWEEN CELLS (IE. PRODUCTION OF PROTEIN RESPONSIBLE FOR CELL ADHESION)
PROTEIN AND OTHER BIOCHEM DATA RESPONSIBLE FOR IBC, TISSUE PROPERTIES, AND ETC.
MALIGNANT ENVIRONMENT
GENETIC INFO NOT SPECIFIC TO META SPREAD
PROTEIN AND OTHER BIOCHEM NOT SPECIFIC TO META SPREAD
STATISTICAL DATA ON CELL PROPERTIES (IE. SIZE, SHAPE, TIMING OF STAGES, SPEED, ETC.)
GENETIC INFO INVOLVED IN STRUCTURE, SHAPE, SIZE OF CELLS, AND ETC.
GENETIC INFORMATION CONCERNING IBC DATA, TISSUE STRUCTURE, TUMOR STRUCTURE, AND ETC. IN A MALIGNANT ENVIRONMENT
PROTEINS AND OTHER BIOCHEM ELEMENTS INVOLVED IN THE INTERACTION BETWEEN CELLS NON-MALIGNANT ENVIRONMENT
GENES RESPONSIBLE FOR CELL SHAPE, SIZE, AND ETC.
STATISTICAL INFORMATION RESPONSIBLE FOR CELL CYCLE, BOND STRENGTH, MEMBRANE STRENGTH, TISSUE STRUCTURE, AND ETC.
STATISTICAL DATA CONCERNING TISSUE STRUCTURE, IBC, AND ETC. MALIGNANT ENVIRONMENT
STATISTICAL DATA ON INTERACTION (BOND STRENGTH, NUTRITION DISTRIBUTION, ETC.)
PROTEINS AND OTHER BIOCHEM COMPOUNDS RESPONSIBLE FOR TISSUE STRUCTURE
DATA CONCERNING THE IBC (IE. NUTRITION CONSUMPTION, N. DISTRIBUTION, COMPOUND CONCENTRATIONS FOR BOND STRENGTH, ETC.)
STATISTICAL DATA ON CELL CYCLE CONTROL AND PHYSICAL PROPERTIES (IE. AVERAGE MEMBRANE STRENGTH AND SHAPE)
(CONTINUED FROM FIG. 11A)
COMPOUNDS NEEDED FOR CELL FUNCTION AND THEIR REQUIRED CONCENTRATIONS
STATISTICAL DATA RELATED TO METASTATIC SPREAD (IE. SITE, SPEED, ETC.)
STATISTICAL DATA CONCERNING CELLULAR ACTIVITY NOT SPECIFIC TO META SPREAD
DATA CONCERNING THE MECHANISMS OF METASTATIC SPREAD
PATIENT INFO DATABASE

FIG.11B

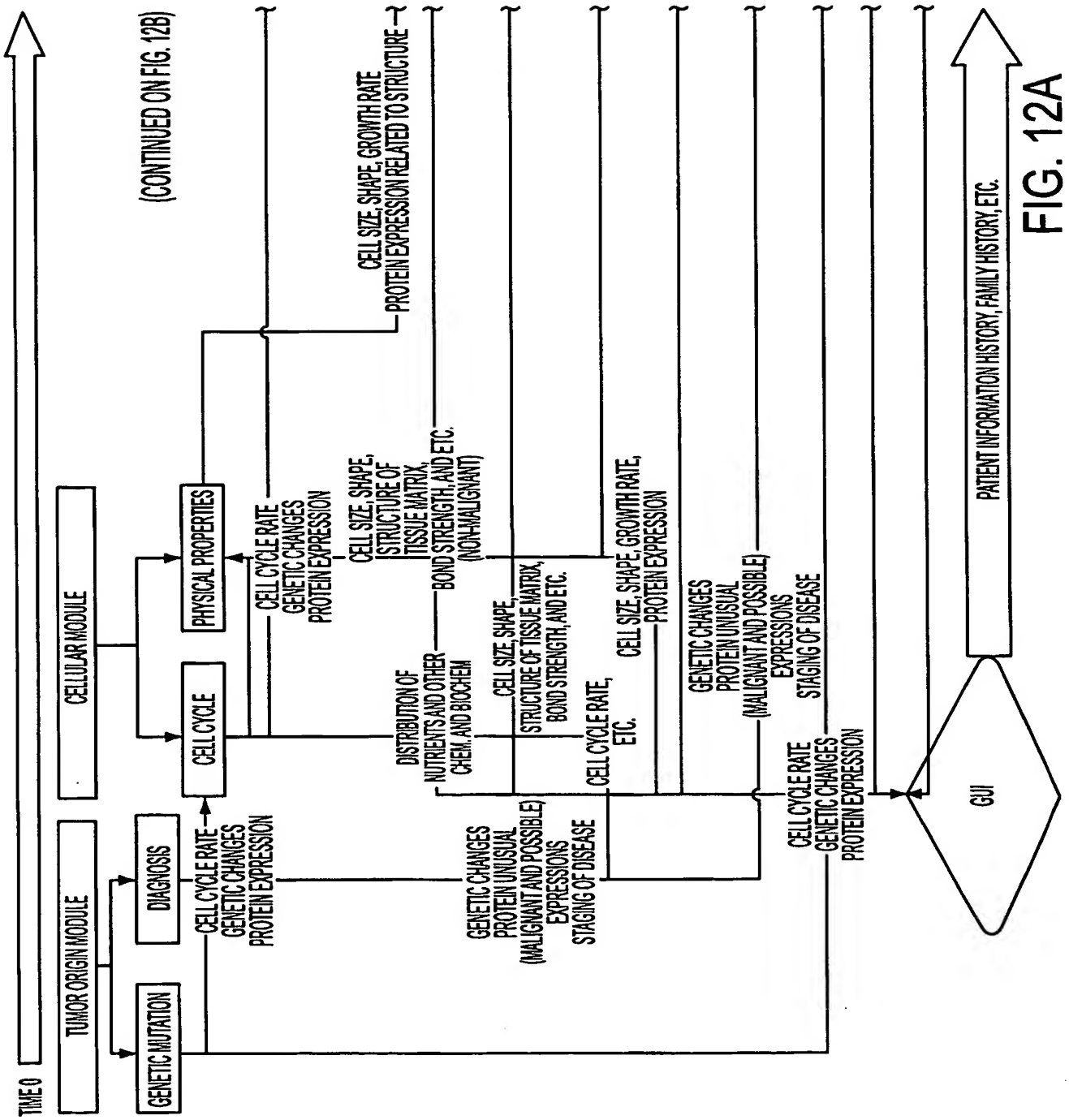
TIME 0
TUMOR ORIGIN MODULE
GENETIC MUTATION
DIAGNOSIS
CELLULAR MODULE
CELL CYCLE
PHYSICAL PROPERTIES
(CONTINUED ON FIG. 12B)
CELL CYCLE RATE
GENETIC CHANGES
PROTEIN EXPRESSION
CELL SIZE, SHAPE, GROWTH RATE
PROTEIN EXPRESSION RELATED TO STRUCTURE
CELL SIZE, SHAPE,
STRUCTURE OF
TISSUE MATRIX,
BOND STRENGTH, AND ETC.
(NON-MALIGNANT)
DISTRIBUTION OF
NUTRIENTS AND OTHER
CHEM. AND BIOCHEM
CELL SIZE, SHAPE,
STRUCTURE OF TISSUE MATRIX,
BOND STRENGTH, AND ETC.
CELL CYCLE RATE,
ETC.
CELL SIZE, SHAPE, GROWTH RATE,
PROTEIN EXPRESSION
GENETIC CHANGES
PROTEIN UNUSUAL
(MALIGNANT AND POSSIBLE)
EXPRESSIONS
STAGING OF DISEASE
CELL CYCLE RATE
GENETIC CHANGES
PROTEIN EXPRESSION
GENETIC CHANGES
PROTEIN UNUSUAL
(MALIGNANT AND POSSIBLE)
EXPRESSIONS
STAGING OF DISEASE
CELL CYCLE RATE
GENETIC CHANGES
PROTEIN EXPRESSION
GUI
PATIENT INFORMATION HISTORY, FAMILY HISTORY, ETC.

FIG. 12A

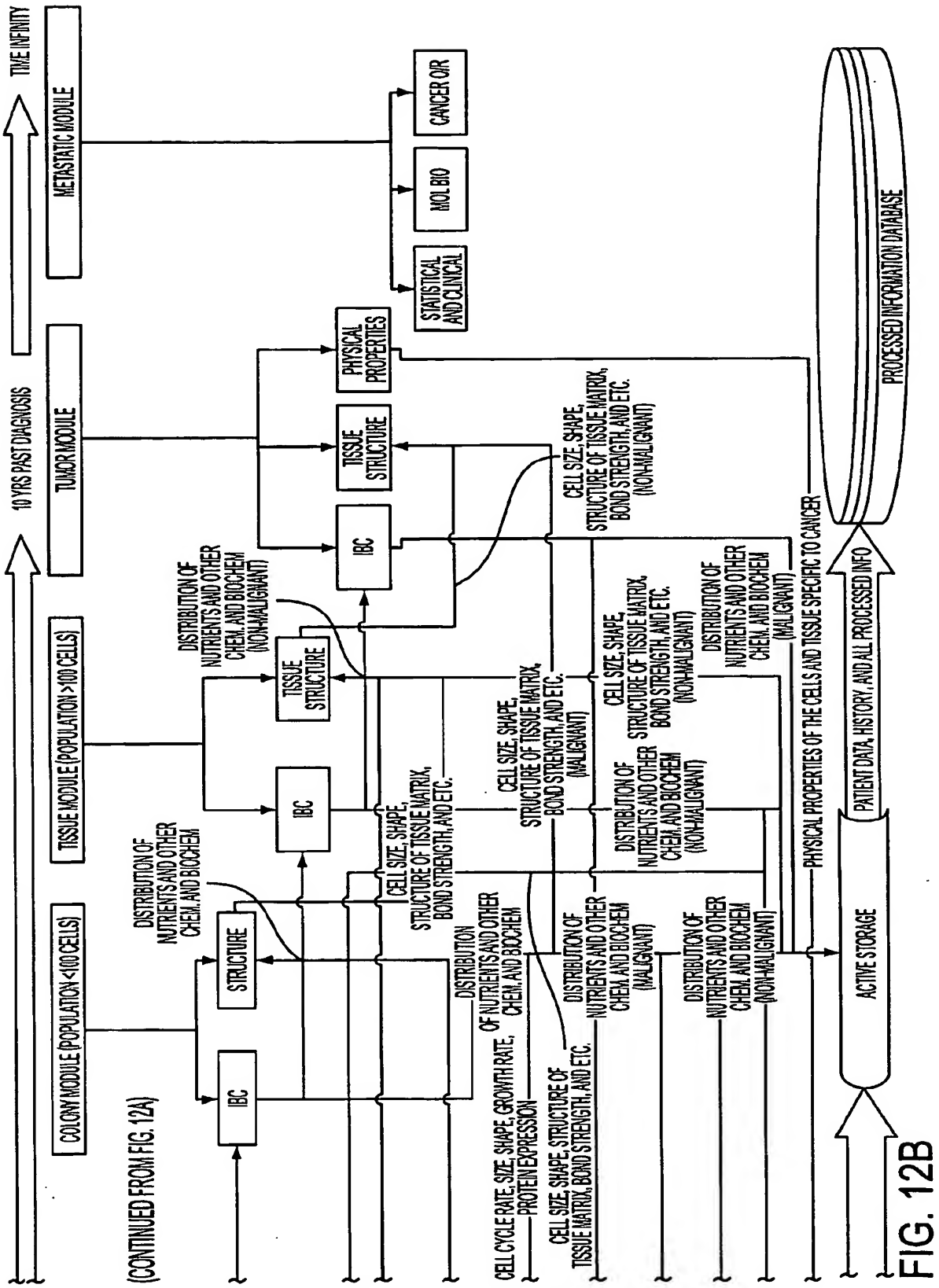
TIME INFINITY
10 YRS PAST DIAGNOSIS
METASTATIC MODULE
TUMOR MODULE
TISSUE MODULE (POPULATION >100 CELLS)
COLONY MODULE (POPULATION <100 CELLS)
(CONTINUED FROM FIG. 12A)
CANCER OR
MOL BIO
STATISTICAL AND CLINICAL
PHYSICAL PROPERTIES
TISSUE STRUCTURE
IBC
STRUCTURE
DISTRIBUTION OF NUTRIENTS AND OTHER CHEM. AND BIOCHEM (NON-MALIGNANT)
CELL SIZE, SHAPE, STRUCTURE OF TISSUE MATRIX, BOND STRENGTH, AND ETC. (NON-MALIGNANT)
CELL SIZE, SHAPE, STRUCTURE OF TISSUE MATRIX, BOND STRENGTH, AND ETC. (MALIGNANT)
DISTRIBUTION OF NUTRIENTS AND OTHER CHEM. AND BIOCHEM (MALIGNANT)
CELL CYCLE RATE, SIZE, SHAPE, GROWTH RATE, PROTEIN EXPRESSION
CELL SIZE, SHAPE, STRUCTURE OF TISSUE MATRIX, BOND STRENGTH, AND ETC.
PHYSICAL PROPERTIES OF THE CELLS AND TISSUE SPECIFIC TO CANCER
PROCESSED INFORMATION DATABASE
PATIENT DATA, HISTORY, AND ALL PROCESSED INFO
ACTIVE STORAGE

FIG. 12B

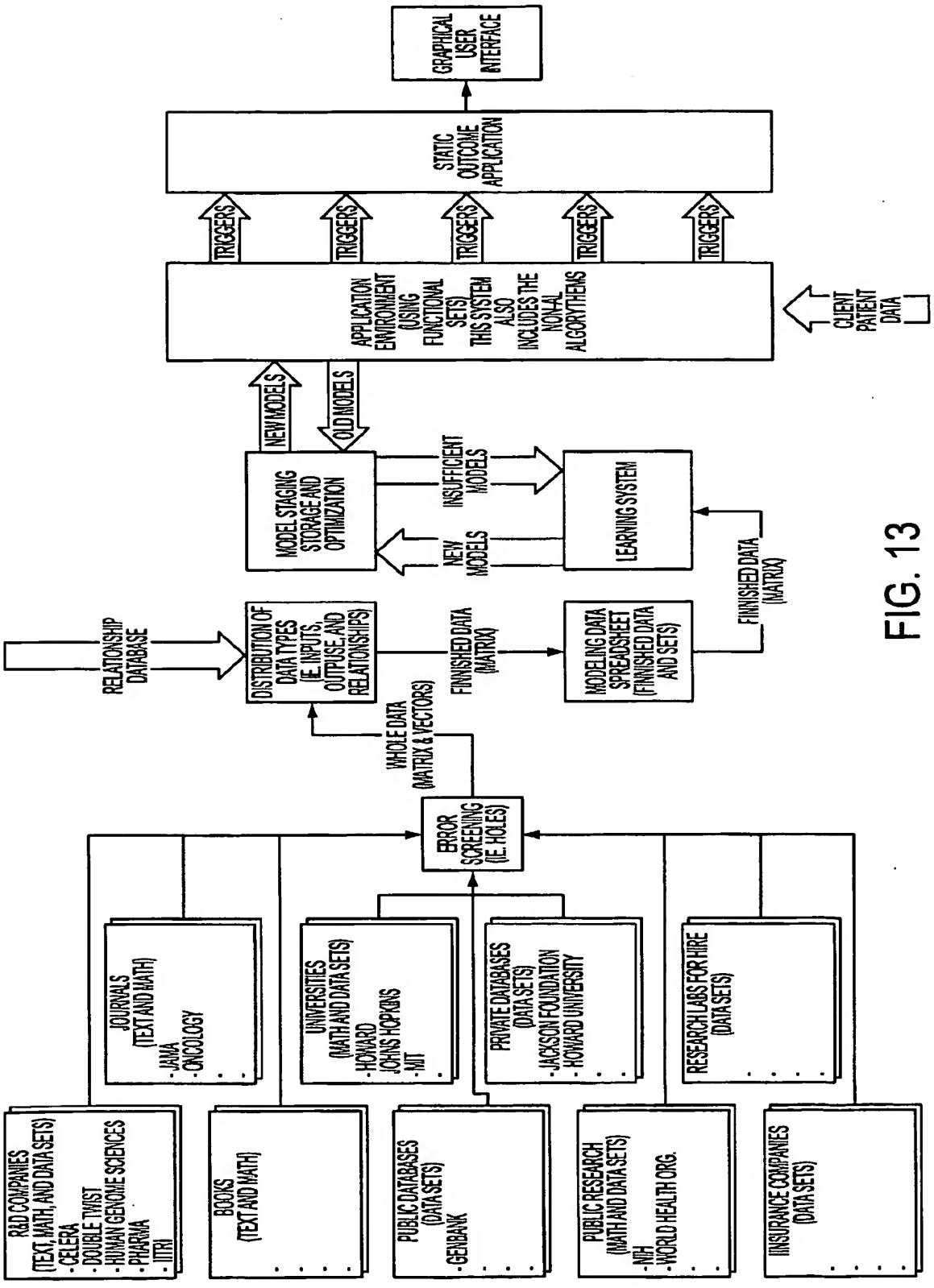
GRAPHICAL USER INTERFACE
STATIC OUTCOME APPLICATION
TRIGGERS
TRIGGERS
TRIGGERS
TRIGGERS
TRIGGERS
APPLICATION ENVIRONMENT (USING FUNCTIONAL SETS) THIS SYSTEM ALSO INCLUDES THE NON-AL ALGORYTHMS
CLIENT PATIENT DATA
NEW MODELS
OLD MODELS
MODEL STAGING STORAGE AND OPTIMIZATION
INSUFFICIENT MODELS
NEW MODELS
LEARNING SYSTEM
FINNISHED DATA (MATRIX)
RELATIONSHIP DATABASE
DISTRIBUTION OF DATA TYPES (IE. INPUTS, OUTPUSE, AND RELATIONSHIPS)
FINNISHED DATA (MATRIX)
MODELING DATA SPREADSHEET (FINNISHED DATA AND SETS)
WHOLE DATA (MATRIX & VECTORS)
ERROR SCREENING (IE. HOLES)
JOURNALS (TEXT AND MATH)
- JAMA
- ONCOLOGY
UNIVERSITIES (MATH AND DATA SETS)
- HOWARD
- JOHNS HOPKINS
- MIT
PRIVATE DATABASES (DATA SETS)
- JACKSON FOUNDATION
- HOWARD UNIVERSITY
RESEARCH LABS FOR HIRE (DATA SETS)
R&D COMPANIES (TEXT, MATH, AND DATA SETS)
- CELERA
- DOUBLE TWIST
- HUMAN GENOME SCIENCES
- PHARMA
- ITRI
BOOKS (TEXT AND MATH)
PUBLIC DATABASES (DATA SETS)
- GENBANK
PUBLIC RESEARCH (MATH AND DATA SETS)
- NIH
- WORLD HEALTH ORG.
INSURANCE COMPANIES (DATA SETS)

FIG. 13

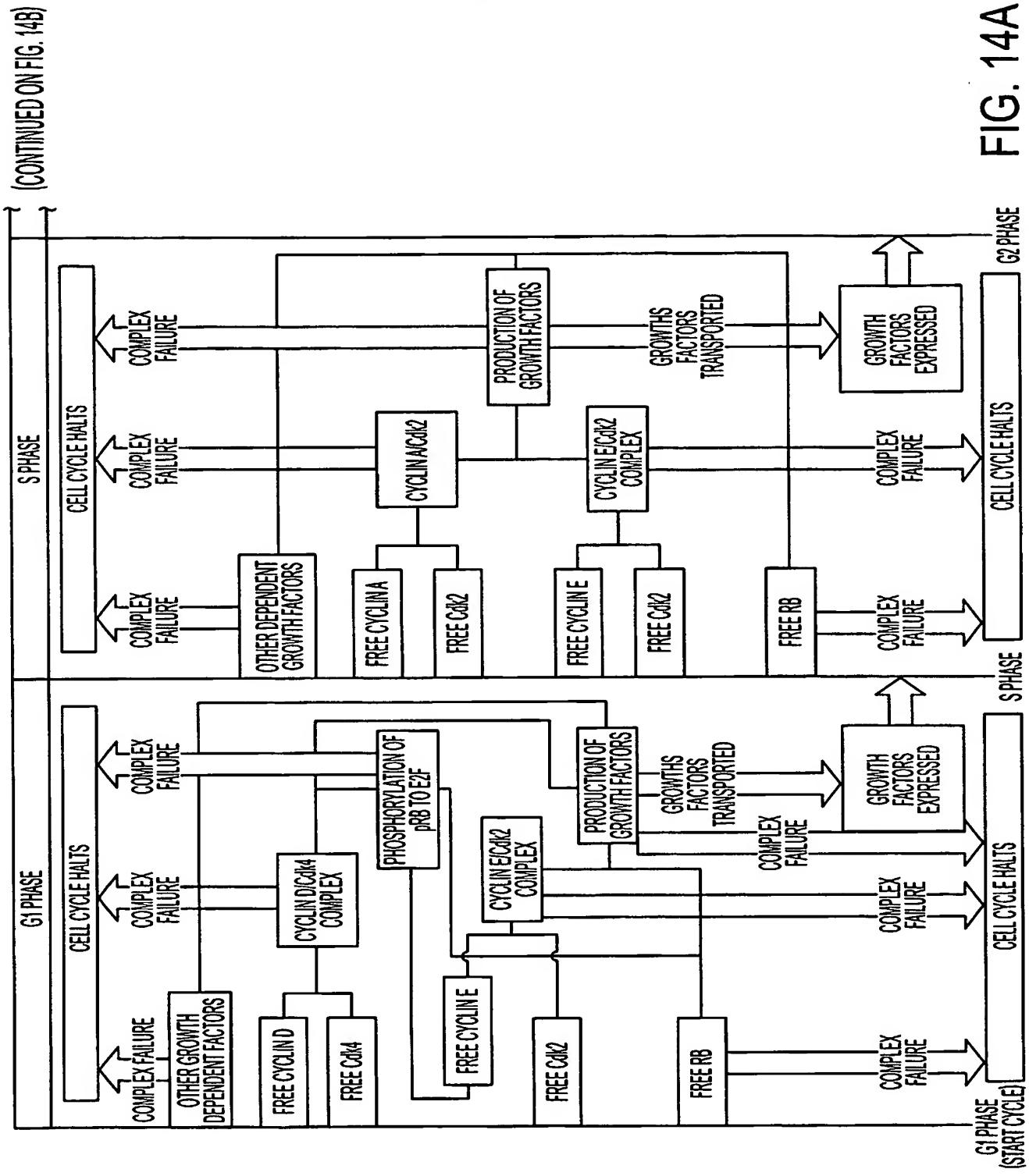
(CONTINUED ON FIG. 14B)
S PHASE
CELL CYCLE HALTS
COMPLEX FAILURE
COMPLEX FAILURE
COMPLEX FAILURE
OTHER DEPENDENT GROWTH FACTORS
FREE CYCLIN A
FREE Cdk2
CYCLIN A/Cdk2
PRODUCTION OF GROWTH FACTORS
GROWTHS FACTORS TRANSPORTED
FREE CYCLIN E
FREE Cdk2
CYCLIN E/Cdk2 COMPLEX
FREE RB
COMPLEX FAILURE
COMPLEX FAILURE
COMPLEX FAILURE
GROWTH FACTORS EXPRESSED
G2 PHASE
CELL CYCLE HALTS
G1 PHASE
CELL CYCLE HALTS
COMPLEX FAILURE
COMPLEX FAILURE
COMPLEX FAILURE
COMPLEX FAILURE
OTHER GROWTH DEPENDENT FACTORS
FREE CYCLIN D
FREE Cdk4
CYCLIN D/Cdk4 COMPLEX
PHOSPHORYLATION OF pRB TO E2F
FREE CYCLIN E
FREE Cdk2
CYCLIN E/Cdk2 COMPLEX
PRODUCTION OF GROWTH FACTORS
GROWTHS FACTORS TRANSPORTED
FREE RB
COMPLEX FAILURE
COMPLEX FAILURE
COMPLEX FAILURE
GROWTH FACTORS EXPRESSED
S PHASE
CELL CYCLE HALTS
G1 PHASE (START CYCLE)

FIG. 14A

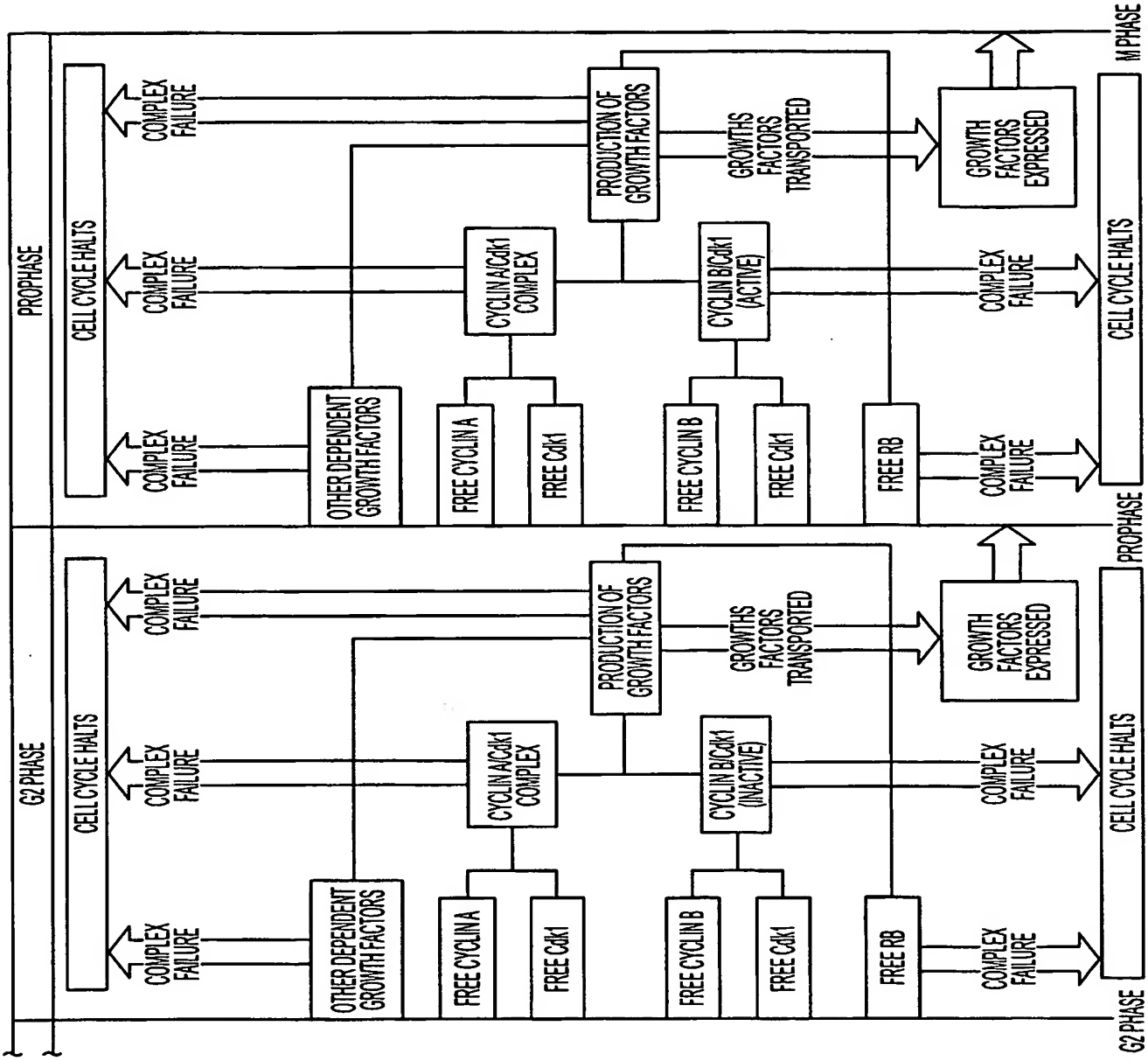
(CONTINUED FROM FIG. 14A)
G2 PHASE
PROPHASE
CELL CYCLE HALTS
COMPLEX FAILURE
COMPLEX FAILURE
COMPLEX FAILURE
OTHER DEPENDENT GROWTH FACTORS
CYCLIN A/Cdk1 COMPLEX
FREE CYCLIN A
FREE Cdk1
PRODUCTION OF GROWTH FACTORS
GROWTHS FACTORS TRANSPORTED
CYCLIN B/Cdk1 (INACTIVE)
FREE CYCLIN B
FREE Cdk1
FREE RB
COMPLEX FAILURE
COMPLEX FAILURE
GROWTH FACTORS EXPRESSED
CELL CYCLE HALTS
PROPHASE
G2 PHASE
M PHASE
CELL CYCLE HALTS
COMPLEX FAILURE
COMPLEX FAILURE
COMPLEX FAILURE
OTHER DEPENDENT GROWTH FACTORS
CYCLIN A/Cdk1 COMPLEX
FREE CYCLIN A
FREE Cdk1
PRODUCTION OF GROWTH FACTORS
GROWTHS FACTORS TRANSPORTED
CYCLIN B/Cdk1 (ACTIVE)
FREE CYCLIN B
FREE Cdk1
FREE RB
COMPLEX FAILURE
COMPLEX FAILURE
GROWTH FACTORS EXPRESSED
CELL CYCLE HALTS

FIG. 14B

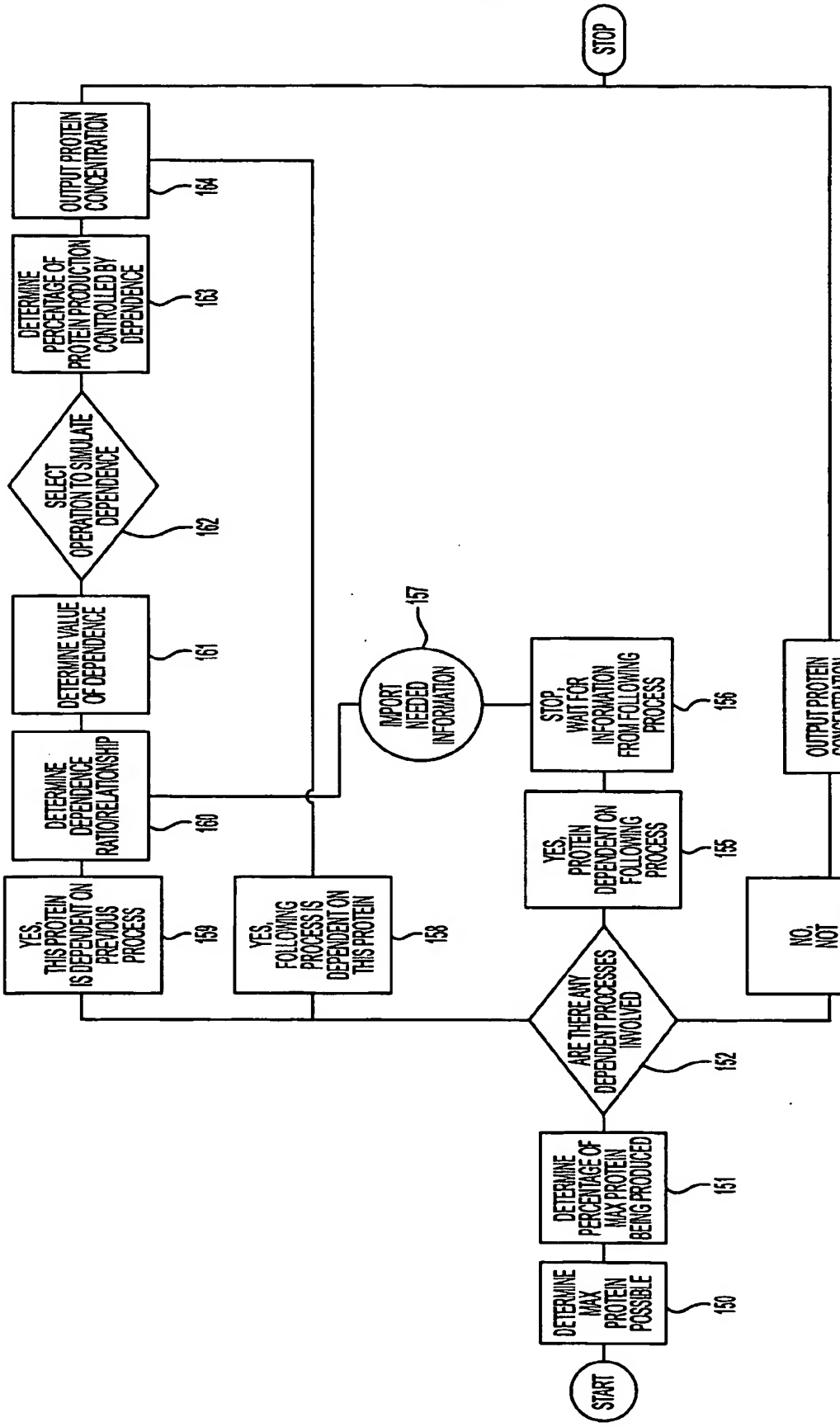
START
DETERMINE MAX PROTEIN POSSIBLE
150
DETERMINE PERCENTAGE OF MAX PROTEIN BEING PRODUCED
151
ARE THERE ANY DEPENDENT PROCESSES INVOLVED
152
NO, NOT DEPENDENT
153
OUTPUT PROTEIN CONCENTRATION
154
YES, PROTEIN DEPENDENT ON FOLLOWING PROCESS
155
STOP, WAIT FOR INFORMATION FROM FOLLOWING PROCESS
156
IMPORT NEEDED INFORMATION
157
YES, FOLLOWING PROCESS IS DEPENDENT ON THIS PROTEIN
158
YES, THIS PROTEIN IS DEPENDENT ON PREVIOUS PROCESS
159
DETERMINE DEPENDENCE RATIO/RELATIONSHIP
160
DETERMINE VALUE OF DEPENDENCE
161
SELECT OPERATION TO SIMULATE DEPENDENCE
162
DETERMINE PERCENTAGE OF PROTEIN PRODUCTION CONTROLLED BY DEPENDENCE
163
OUTPUT PROTEIN CONCENTRATION
164
STOP

FIG. 15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/17810

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :435/7.1, 6; 705/2, 3; 706/45; 16; 707/1, 3;
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/7.1, 6; 705/2, 3; 706/45; 16; 707/1, 3;

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,594,637 A (EISENBERG et al) 14 January 1997, entire document.	1-5
Y	US 5,858,683 A (KEESEE et al) 12 January 1999. entire document.	1-5
A	US 5,794,208 A (GOLTRA) 11 August 1998, entire document.	1-5
A	US 5,800,350 A (COPPLERSON et al) 01 September 1998, entire document.	1-5
A	US 5,756,294 A (WHITE et al) 26 May 1998, entire document.	1-5
A	US 5,724,580 A (LEVIN et al) 03 March 1998, entire document.	1-5

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
13 AUGUST 2000	03 OCT 2000

Name and mailing address of the ISA/US	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/17810

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,867,821 A (BALLANTYNE et al) 02 February 1999, entire document.	1-5
A	US 5,790,761 A (HESELTINE et al) 04 August 1998, entire document.	1-5
A	US 5,517,405 A (MCANDREW et al) 14 May 1996, entire document.	1-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/17810

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

A61B 5/00; C12Q 1/68; G06F 17/30, 15/18, 159/00; 17/60; G01N 33/53

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

EAST,STN
educating,estimating,describing,predicting,cancer,metastases,peocess,stages,develops,presence,algorithm,mathematical,programs,software